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BUREAU OF HYGIENE AND TROPICAL DISEASES.

TROPICAL DISEASES BULLETIN.

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SUMMARY OF RECENT ABSTRACTS.*

III. MALARIA.

Epidemiology.

Greece, especially Epirus, is stated by PAMPANA (p. 427) to be the most malarious country in Europe. Blackwater fever is common. Malaria is endemic, even in cities, but from time to time epidemics, which depend on weather conditions, break out. Heavy rainfall in the early part of the year is followed by summer epidemics. The malaria season is at its height from August to October, and, as usual, *P. vivax* is prominent in the early part of the season, and *P. falciparum* in the late. In epidemic years *P. falciparum* is prominent throughout. *P. malariae* is found fairly frequently in non-epidemic years, but is relatively unimportant in epidemics. [A malaria map of Greece is included in the original abstract.]

CASINI (p. 286), COLUZZI (p. 287) and PELAZZI (p. 287) write of malaria in Albania. It is widespread along the coast, and near rivers and mountain streams to a height of 3,600 feet. The principal vector is *A. maculipennis* var. *sacharovi* (*elutus*), but *A. superpictus* is important inland. The peak malaria season is from August to October, and at this time *P. falciparum* infections are more common than *P. vivax*. *P. malariae* is much less common.

PAMPANA (p. 429) states that, except for some mountainous areas and some coastal islands, the whole of Yugoslavia is malarious; the highest incidence is in South Serbia and the Danubian plain. The vectors, and the endemic periodicity of the various forms of the disease are similar to those which occur in Greece.

PARROT *et al.* (p. 739) have investigated an area near Constantine, Algeria, where malaria is endemic, with occasional epidemics. *A. maculipennis* var. *labranchiae* breeds abundantly in canals and ditches.

* The information from which this series of summaries has been compiled is given in the abstracts which have appeared in the *Tropical Diseases Bulletin*, 1943, v. 40. References to the abstracts are given under the names of the authors quoted, and the pages on which the abstracts are printed.

P. falciparum is the commonest parasite found at all ages, and is concerned in the epidemic outbreaks. Premunition against *P. falciparum* is much shorter and less effective than that against *P. vivax* or *P. malariae*, and, during an epidemic, the proportion of carriers of gametocytes of *P. falciparum* increases considerably, whereas the proportion of carriers of gametocytes of *P. vivax* and *P. malariae* remains almost unchanged.

In describing an outbreak of malaria in the Department of Constantine, Algeria, CLASTRIER (p. 741) remarks that important factors affecting the severity of the epidemic were the state of under-nourishment of the population as a result of bad harvests, and the fact that the outbreak coincided with the month of Ramadan, during which, according to Mohammedan law, no food may be taken, and no drugs given by the mouth, between sunrise and sunset.

COLLIGNON (p. 105) gives an account of an epidemic of *P. falciparum* malaria in the Department of Algiers in 1939; he also (p. 430) notes that the deficient rainfall of 1940 and 1941 resulted in a low incidence of malaria in that Department during 1941.

SIEGFRIED and IZAC (p. 738) describe the malaria of Laghouat, south of the Atlas mountains; the disease is not common, but occurs in some oases and after periods of heavy rainfall.

BOURGUIGNON (p. 103) writes of malaria at Elisabethville in the Belgian Congo. *P. falciparum* is the commonest parasite, and there is a well-marked seasonal incidence on this high Katango plateau. The rainy season is from November to April, and the disease reaches its peak in March to May. Seasonal variation depends on the densities of *A. gambiae* and *A. funestus*.

A number of other papers on malaria in the Belgian Congo have been abstracted during the year. These consist largely of surveys of various districts, and are chiefly of local interest. The references are as follows:—BARLOVATZ (p. 101); SCHWETZ (pp. 102, 212); SCHWETZ and BAUMANN (pp. 103, 211, 212); SCHWETZ *et al.* (pp. 213, 357, 743); NICOLAY (p. 104); DUREN (pp. 210, 743); VAN WYMEERSCH and TROLLI (p. 213).

In spite of a general opinion that malaria is not contracted in Addis Ababa (altitude 2,500 metres), MARTIN (p. 744) describes 4 cases of local infection. *A. gambiae* breeds in a river bed after the rainy season, but never, apparently, in permanent collections of water.

As a result of investigations in Ceylon, extending over three years, SIVALINGAM (p. 746) has found that when the incidence of malaria is low, *P. malariae* is most in evidence, but that during seasonal or epidemic increases *P. falciparum* and *P. vivax* become more prevalent, the former being dominant during epidemics. In his opinion an increase to 50 in the percentage incidence of *P. falciparum* heralds a severe outbreak of malaria.

NICHOLS (p. 579) shows to what extent malaria has diminished as a cause of death in the United States since 1900. The decrease has been most marked since 1937 and is, no doubt, due to the vigorous antimalarial measures carried out in the Southern States. FAUST and DE BAKEY (p. 664) publish a graph showing the trends of malaria mortality in the United States from 1929 to 1940. The expected cyclical increase in 1938–40 did not occur, and rates have fallen fairly steadily since 1933–36, the years of the depression. The malaria death rate is a reflection of *P. falciparum* malaria, but there is reason to believe that *P. vivax* malaria has also decreased.

Aetiology.

KIKUTH (p. 284) gives an account of the newer knowledge of the process of development of malaria parasites from the time of inoculation of sporozoites into the vertebrate host, particularly mentioning the possible course of development of the unpigmented exoerythrocytic forms. He concludes that the goal for further investigation is the discovery of a causal prophylactic against the sporozoites or against the exoerythrocytic schizonts which arise from the sporozoites.

HUFF *et al.* (p. 815) propose the name cryptozoite for the first generation of the malaria parasite developing from a sporozoite. This would cover all stages of development after the entry of the sporozoite into a cell (other than an erythrocyte) up to the mature schizont.

KITCHEN and PUTNAM (p. 109) have studied the cycle of *P. falciparum* by daily observations made on negroes infected by mosquito bite or by inoculation of infected blood. The cycle appears to be very stable. The timing of first appearance, and of peak density, of trophozoites and gametocytes was virtually identical in naturally infected patients. The timing of key points may be altered in individual patients by natural resistance, acquired immunity, or treatment, but there are indications that if one interval is lengthened the next is shortened, and the cycle is brought back into line. This leads to the belief that events in the cycle are determined before the appearance of trophozoites in the peripheral blood, and possibly at the time of inoculation. The sexual forms probably arise from the segmenting asexual parasites, but the production of gametocytes probably begins before the end of the prepatent period. The interval of about 10 days between the first appearance (and between the peak densities) of trophozoites and gametocytes indicates that the gametocytes require a period for development over and above that needed for them to accumulate sufficiently to reach microscopic visibility.

Transmission.

ZUMPT (p. 7) discusses the races of *Anopheles maculipennis*, of which seven have been distinguished in Europe. In view of the restrictions on interbreeding imposed by physiological differences and by lack of mutual inclination of the various races to pair, he suggests that they should be accorded specific rank.

RODHAIN and VAN HOOF (p. 214) note that in Belgium *A. maculipennis* var. *atroparvus*, probably the only vector of malaria, breeds not only in slightly brackish waters along the coast, but also in certain inland localities where the water is quite fresh. HILL *et al.* (p. 818) remark that in Portugal, rice fields form the breeding places of enormous numbers of *A. maculipennis* var. *atroparvus*, here also the vector of malaria.

MESSERLIN (p. 742) notes that in Morocco anophelines have been found at least 8 or 9 kilometres away from their breeding places. [The species are not named, presumably they were *A. maculipennis* var. *labranchiae*.]

BEKLEMISHEV (p. 511) gives an account of his studies on the life history of *A. maculipennis* and other blood-sucking arthropods. LAVRENKO (p. 510) describes a method for the identification of the larvae of three races of *A. maculipennis*. SKOPIN (p. 287) reports the dates of the various stages of development of *A. maculipennis* in

Kazakistan, and in particular the dates and circumstances of emergence from hibernation. GORITZKAYA (p. 433) produces evidence which shows that mosquitoes (*A. maculipennis*) responsible for the first fresh cases of malaria in Southern Russia may belong to the generation which has overwintered, or to the succeeding generation, but the latter are the more important.

In Greece the important vectors are *A. maculipennis* (*typicus*, *messeae* and *sacharovi*) and *A. superpictus*. PAMPANA (p. 427) states that the latter, which reaches its peak density later than *sacharovi*, is the more efficient vector, but *sacharovi* is the more anthropophilic.

SAUTET (p. 110) gives a list of the Anopheles of Syria and Lebanon. *A. claviger* is the only vector of malaria in southern Lebanon; elsewhere *A. m. sacharovi*, *A. superpictus*, *A. sergenti* and *A. multicolor* are responsible for transmission.

SALITERNIK (p. 287) has studied the egg patterns of the nine species of Anopheles found in Palestine.

LEWIS (pp. 288, 665) records *A. gambiae* as far north as Wadi Halfa near the Egyptian border. SCHWETZ (p. 7) notes that *A. gambiae* is generally absent at altitudes over 5,000 feet in the region of Lake Kivu and Lake Albert, in the Belgian Congo.

A. gambiae breeds in water fully exposed to sunlight. HADDOW (p. 816) has shown that the water in the breeding places of *A. gambiae* reaches much higher temperatures, and undergoes much greater temperature fluctuations, than the shaded water in which *A. funestus* breeds.

Writing of *A. gambiae* in Brazil, CAUSEY *et al.* (p. 580) point out that only the light-coloured variety was seen. This mosquito behaved as it does in Africa, breeding in fresh water exposed to the sun, usually near human dwellings, and, in the adult stage, showing marked anthropophilism. The infection rate in the experimental areas was 5·6 per cent., compared with 1·5 per cent. in species of the *tarsimaculatus* group. DEANE and CAUSEY (p. 581) investigated the viability of eggs of *A. gambiae* kept in moist or drying shaded sand or mud. After 18 days only 1 per cent. or less had survived. If, however, the female mosquitoes were kept at 10–13°C. for 3 days or more after a blood meal, they laid abnormal eggs which, in certain respects, resembled the resistant winter eggs of *A. walkeri* [see PETERS, below]. CAUSEY *et al.* (p. 815) studied the effect of the advent of *A. gambiae* to an area in Brazil previously almost free from malaria. Parasite rates rose to 85·7 per cent., and were similar in adults and children; the increase was parallel to the increase in density of *A. gambiae*, and was occasioned largely by infections with *P. falciparum*. After eradication measures were commenced the parasite and spleen rates were rapidly reduced.

BLACKLOCK and WILSON (p. 358) have observed that, in houses of a West African village, although *A. gambiae* was the most prevalent anopheline in the period April–July, *A. funestus* was the commoner during September–December. *A. gambiae* breeds in small collections of water during the rains, but *A. funestus* breeds in springs which function only after the rains have persisted for some time. DE MESQUITA (p. 744) gives information on malaria in Angola, where the vectors include *A. gambiae* and *A. funestus*. DE MEILLON (p. 110) reports on *A. gambiae* and *A. funestus*, the vectors of malaria in the colony of Mozambique, and (p. 111) gives a list of the other Anopheles found. In only one area was neither of these two species present; there, at an altitude of 1,260 metres, malaria was apparently absent.

RAO (V. V.) *et al.* (p. 9) describe the swarming of *A. sundaicus* and *A. subpictus* ; they note that the former flew two miles from the breeding place to the swarming place.

RUSSELL and RAO (T. R.) (pp. 8, 435) describe the swarming, mating and oviposition of *A. culicifacies*. Having observed that larvae of *A. culicifacies* are found in rice fields only when the plants are less than a foot in height, they determined by experiment that the cause of the absence of larvae and eggs when the plants were over this height was probably the mechanical obstruction offered to ovipositing females by the plants, and not to the shading of the water by the plants. It is the habit of the female to hover a few inches above the water surface, without touching it, in the process of egg-laying and this hovering is presumably prevented by the growing rice or other similar obstruction. Certain other species of Anopheles were much less reduced by these obstructions.

These workers (p. 288) have also studied the life span of *A. culicifacies* ; the average is four days, but in each batch there were always a few individuals which lived much longer than the rest. In a comparison between a malarious and a non-malarious area, in each of which *A. culicifacies* was present, they (p. 289) found that the density of this mosquito was 3–4 times as great in the malarious as in the non-malarious district. They argue that the density of the vector is the chief factor in determining the presence of malaria under these conditions, an opinion in line with Ross's view of a critical density below which transmission does not occur.

ROY and BISWAS (p. 112) found 6 of 719 *A. pallidus* and 5 of 881 *A. culicifacies* with sporozoite infections in Udaipur State, Central Provinces, India. They emphasize the importance of the former as a vector.

In an account of malaria in the Nilgiris District of the Madras Presidency, RUSSELL and JACOB (p. 105) note that the only important vector is *A. fluviatilis*, which breeds in rice fields, irrigation channels, hill streams, river edges, spring pools and wells. In Nilgiris East they found *A. fluviatilis* breeding throughout the year, but in Nilgiris West the very heavy rainfall caused this species almost to disappear from July to September. This mosquito is usually found at altitudes not exceeding 4,000 feet, and adults were most commonly captured in human dwellings ; oöcyst and sporozoite rates of 9·7 and 10·1 per cent. were found, but in one hyperendemic area weekly sporozoite indices ranged from 1·5 to 34·8. It seems that there can be few, if any, more effective vectors of malaria than *A. fluviatilis*. No other infected species were found. Spleen rates varied with altitude :— 1,200–2,000 feet 78·1, 2,000–4,000 feet 50·4 ; above and below these heights the numbers were small. *P. malariae* was the most common species in Nilgiris East (less common in Nilgiris West) and produced the greatest proportion of enlarged spleens.

COVELL and PRITAM SINGH (p. 663) state that, near Lake Chilka in the coastal belt of Orissa, where malaria is hyperendemic, *A. sundaicus* is the only vector of importance. It is well known that this mosquito breeds in saline water, and the optimum salinity appears to be from 600 to 800 parts per 100,000. The authors found, however, that the presence of putrefying algae and other vegetation favours breeding, and that salinity is important only in so far as it promotes the growth of vegetation. If pools and tanks can be kept free from weeds,

breeding can be eliminated, and this promises to be the most successful method of combating malaria in this region.

IYENGAR (p. 663) has noted that, in the delta region of Bengal, areas with a high subsoil water level during the rainy season are much less malarious than areas with a low subsoil water level. *A. philippinensis* is the vector, and breeds in ponds, yet there is no marked difference in the number and variety of such ponds in the areas in question. Nevertheless the prevalence of *A. philippinensis* was much less in the less malarious villages, but it is not known in what way the high subsoil water acts as a deterrent to the breeding of this mosquito.

THOMSON (p. 747) has previously noted that in the laboratory larvae of *A. minimus* will develop in water far more heavily polluted with organic matter than the female will accept for oviposition, and has now confirmed these findings by field experiments. He has devised a new analytical method (estimation of oxygen absorbed from *alkaline* permanganate) to investigate the qualitative differences in organic matter. Some rice fields and collections of stagnant water contain enough organic matter to repel *A. minimus*, but this is not true of other collections which the mosquito avoids, so that, evidently, the quantity of organic pollution does not provide the whole explanation, though the quality of the organic matter may be a factor.

The same author (p. 748) has shown that *A. minimus* will not lay eggs in water fully exposed to sunlight, and that wells with vertical sides, and with vegetation at the water edge, in which the mosquito breeds prolifically, may be rendered almost free by removing the vegetation and converting the vertical walls into smooth sloping sides.

In spite of the fact that 21 species of Anopheles have been identified in south-western Yunnan, some of which are vectors of malaria in other parts of the world, SWEET *et al.* (p. 666) report that *A. minimus*, which is the most prevalent species, is the only one found infected, at a rate of 0·9 over a period of 16 months. Infection rates were highest from August to November, and there is, apparently, no transmission in January and February.

LEVER (p. 816) notes that *A. punctulatus*, the vector of malaria in Melanesia, is not known to be present in Fiji. In view, however, of the great variety of its breeding places it could easily establish itself in Fiji, and the greatest vigilance will be necessary to prevent this.

HURLBUT (p. 748) has calculated the rate of growth of *A. quadrimaculatus* in relation to temperature, and estimates that in northern Alabama there should be 9 or 10 generations each year.

EYLES and BISHOP (p. 817) have shown that *A. quadrimaculatus* can travel a distance of 2½ miles, and CLARKE (p. 748) has shown that it can travel 8 miles, and *A. punctipennis* 10½ miles.

EYLES and BISHOP (p. 667) have found that the movements of *A. quadrimaculatus* out of buildings at dusk and into buildings after sunrise are correlated with the light intensity. During the day the buildings are cooler and more moist than the open air, and evaporation is therefore less indoors, where the mosquitoes spend the daytime.

The inhabitants of the Okefenokee swamp, Georgia, United States, are free from malaria, though the disease is common in the surrounding regions. FROHNE (p. 215) shows that the water of the swamp is very acid, that sphagnum moss is abundant, and that *A. crucians* is the only anopheline found breeding. The common vector of malaria, *A. quadrimaculatus*, is absent. He relates these findings to the desmid content of the swamp water, which is very high.

PETERS (p. 749) points out that *A. walkeri* differs from other North American species in that it overwinters in the egg stage. The winter egg differs from the summer egg in certain respects ; it is larger, the floats are longer, and a reticulated exochorion extends over the dorsal surface. The winter eggs remain viable even if kept moist at a temperature of —21°C. for 72 hours.

BANG *et al.* (p. 817) have shown that the entry of *A. walkeri* into human habitations at night is largely due to attraction towards artificial light, and not to the presence of human beings. The general installation of electric light in rural areas, therefore, may cause the mosquito to become a vector of some importance.

CARR and HILL (p. 745) give an account of malaria in Cuba, where the disease is only moderately prevalent. This relative freedom they ascribe to the remarkable porosity of the soil on underlying limestone. Small local epidemics are usually due to man-made breeding places. *A. albimanus* is probably the chief vector, but *A. crucians* is probably, and *A. vestitipennis* possibly, concerned in transmission.

In a survey of El Salvador, Central America, SÚTTER and ZUNIGA (p. 107) found that splenic indices and parasite rates were highest at low levels of altitude, and that *A. albimanus*, the only proved vector in the area, is an inhabitant chiefly of the lowlands. The incidence of the three malaria parasites was almost the same ; *P. falciparum* and *P. malariae* were more commonly associated with the larger spleens than was *P. vivax*. KUMM and ZUNIGA (p. 108) have studied the mosquitoes of El Salvador ; eight species of Anopheles were found. *A. albimanus* (the only known vector in this area) is a lowland mosquito and is especially prevalent in the rainy season.

BUSTAMANTE *et al.* (p. 453) have found, for the first time, *A. darlingi* in the Yucatán peninsula. BEVIER (p. 512) reports the first stages of an enquiry into the breeding of *A. darlingi*, the only important vector in the coastal region of British Guiana. UNTI and RAMOS (p. 514) remark that in southern Brazil *A. darlingi* may be found up to an altitude of 1,000 metres. UNTI (p. 515) notes that in Brazil, although it does not appear that the *p*H of breeding waters explains the vagaries of anopheline and malaria distribution, yet certain species do exhibit preferences ; *A. darlingi*, for instance, has a marked preference for neutral or slightly alkaline water.

CORRÊA and RAMOS (p. 513) give an account of the Anopheles of the State of São Paulo, Brazil.

ALBERTO ALVARADO (p. 745) gives a description of malaria in Argentina. *A. pseudopunctipennis* is the chief vector in the north-east, but has been reduced recently by the control measures taken. In the Litoral area *A. albitarsis* appears to be concerned. It is noted that in Argentina infections with *P. falciparum* are unusually mild.

DA FONSECA and CORRÊA (p. 516) note that although *A. cruzi* has long been suspected as a potential vector of malaria, proof has not hitherto been obtained. They have now succeeded in infecting two of 29 specimens with *P. vivax*. AMARAL (p. 289) has found oöcysts in *A. cruzi* and *A. bellator* in Paraná.

FONSECA (p. 515) has infected *A. eiseni* with *P. falciparum* in the laboratory, but does not consider that this mosquito is likely to be an important vector of malaria in Brazil because it is not an avid blood-sucker of man (and certain other animals).

ROY and GANGULI (p. 749) describe their method for preparing precipitating sera for determining the nature of the stomach contents of blood-sucking insects, and the technique of the precipitin test.

Pathology.

KNISELY *et al.* (p. 584), and LACK (p. 676) have studied the process of intravascular agglutination of parasitized red cells in malaria. A layer of fibrin, or similar substance, is deposited on the cells, causing them to stick together, but not to the endothelium. Plasma viscosity increases and flow is reduced. The circulatory damage resulting from these changes includes anaemia, haemoconcentration, anoxia and their sequelae. RIGDON (p. 436) writes of the importance of tissue anoxaemia in malaria. This is the result of the rapid destruction of red cells, and of a high degree of parasite infection of the remaining red cells. A temporary lack of oxygen causes increased capillary permeability and this results in haemoconcentration. The manifestations of anoxaemia are similar to those of shock. In a study of cardiac lesions in malaria MOHR (p. 10) notes that the finer capillaries may be partly or completely blocked by accumulation of parasites, with injury to the endothelium and malnutrition of the muscle supplied by these capillaries. In the early stages of such damage treatment may restore the tissues to normal, but if neglected, permanent mischief may be done, with dilatation of heart or aorta.

KOPP (p. 10) has noted that the onset of malaria is accompanied by rapid, progressive and marked reduction of plasma albumin ; but that globulin and fibrinogen fluctuations show no consistent trends. It is probable that the infection interferes with the synthesis of albumin by the liver, and increase in globulin may be due to destruction of red cells. Fever produced by injection of typhoid vaccine or by the inductotherm did not produce comparable effects.

Immunity.

BOYD (p. 11) has observed the course of malaria in 388 white patients infected therapeutically with the McCoy strain of *P. vivax* by means of infected mosquitoes. He notes that 69 others failed to acquire infection in spite of bites by infected mosquitoes. The attacks, in patients who did not experience remissions, did not last more than 70 days, and in patients who had previously acquired autochthonous immunity homologous or heterologous to the strain used for inoculation, subclinical or self-limited attacks lasting less than two weeks occurred. The duration of the attacks varied with the parasite counts in the blood. The parasite rate may become high, and decline slowly (in susceptible persons), or may decline rapidly after a short clinical attack (in persons with some immunity), or the protective mechanism may be vigorous enough to check the rise of parasites before clinical levels are attained. It seems, therefore, that a partly sensitized immune mechanism may be activated gradually, or that a fully sensitized immune mechanism may be activated promptly, by reinfection.

BOYD and KITCHEN (p. 818) note that recovery from an attack of *P. vivax* malaria results in very potent immunity to the homologous strain [the authors evidently refer to spontaneous recovery, or at least to attacks which last for a number of paroxysms. In their paper they

do not refer to malaria treated within a few days.] They have attempted to hyperimmunize convalescent patients by injecting trophozoites and have found that it is not desirable to begin the injections so long as the primary parasitaemia remains at microscopic levels. The first few injections may be followed by subclinical parasitaemia, but later no parasites may be found after the injections; at this point the patient is hyperimmune and can withstand a dose of parasites many million times as great as the minimum infecting dose, without symptoms or parasitaemia. Experiment indicated that this hyperimmunity could not be ascribed to circulating antibodies.

HILL *et al.* (p. 818) have studied malaria in a rice-growing area of Portugal, where *P. falciparum*, *P. vivax* and *P. malariae* are found. They note the gradual development of immunity in childhood.

BOULNOIS (p. 741) notes that Senegalese troops, from the Ivory Coast and French Guinea, stationed near Bone (Algeria), did not acquire malaria, although no precautions were taken, whereas French and Algerian troops stationed nearby were constantly attacked. Comment is made on the state of premunition of the Senegalese [presumably effective even when they were exposed to new strains].

DJAPARIDZE (p. 431) discusses immunity in the people of the Black Sea coast of the Caucasus, where the three principal malaria parasites occur. The infections are seasonal, and the premunition developed is strictly strain-specific. The immunity against *P. vivax* is more stable than that against *P. falciparum*, and whereas the former parasite is the commonest in the blood of children, the reverse is the case in adult life. Adult immunity is reflected in the absence of severe forms of disease and in the presence of infected persons who show no symptoms.

Clinical Findings.

LINDSAY (p. 878) draws attention to the malignancy of pernicious malaria, quoting his experiences in a valley noted for the severity of the disease. Pernicious malaria may be an acute emergency in which even minutes may count. The four main types are algid (the patient cold, pulseless and often unconscious), cerebral (the patient either comatose or restless—even violent), haemorrhagic (with bleeding into the skin or from the nose or bowel), and gastro-intestinal (with vomiting, hiccough, colic or choleraic symptoms). Intravenous quinine is indicated in all these forms of malaria, and the author's rule has been to give intravenous quinine to all patients brought in unconscious, no matter what other treatment may be needed. Quinine intramuscularly is absorbed more slowly than when given by mouth, and has no place in the treatment of pernicious malaria, except in young children. The author remarks that "a microscope has little place in the diagnosis of pernicious malaria. A negative blood-slide has sent many to the grave." [The emphasis of this short paper is on the acute danger of pernicious malaria (presumably due to *P. falciparum*) and on the necessity for immediate drastic treatment. The author states that his conclusions "are not meant to have any wider application than to that place, that community, and that period"; nevertheless, medical officers on active service would do well to bear them in mind.]

ECKSTEIN (p. 516) describes the various clinical types of malaria in children, which include forms simulating intestinal diseases, malarial nephritis and cirrhosis of the liver. He also (p. 517) subdivides the

affections of the nervous system (usually due to *P. falciparum* infections) into categories which include comatose, neuritic, hemiplegic, neuropathic and psychotic forms.

GONTAEVA (p. 436) describes a severe form of benign tertian malaria which occurs in children in central Russia. There is a sudden appearance of cerebral symptoms, and sudden death often takes place before treatment can be given. The only effective treatment is immediate injection of atebrin or quinine. The history of these patients suggests a benign tertian infection in the previous autumn and relapses during the current year. TAREYEV (p. 668) also describes this fulminating form of *P. vivax* malaria, which he distinguishes from the well-known forms of cerebral malaria due to *P. falciparum*. The onset is sudden, with shivering, vomiting, severe headache, convulsions, coma, Cheyne-Stokes respiration and death in 2–3 hours. No definite explanation can yet be given for this syndrome, but it is suggested that it may be due to anoxaemia of the brain; cases of meningitis or mushroom poisoning have been mistaken for it, and some cases may resemble heat stroke. The patients may be saved by injection of quinine or atebrin.

SCHOENBACH and SPINGARN (p. 359) make the point that malaria in drug addicts, acquired by the use of a common syringe for intravenous injection of heroin, rarely conforms to the typical clinical picture of malaria. Suspicion should be raised in patients showing signs of venepuncture, thrombosed basilic veins and irregular fever.

JAVETT and SACKS (p. 216) and KILHAM (p. 217) describe cases of meningococcal septicaemia which simulated malaria in that tertian or quartan periodicity of fever was present. Leucocytosis was a feature in each case.

HEILIG and VISWESWAR (p. 360) describe a case in which general oedema (associated with urinary signs of nephritis) disappeared after treatment with quinine; no parasites were found in the blood. In a second case in which oedema disappeared after treatment with diuretics, ascites persisted but finally disappeared on treatment with quinine. DUTT (p. 668) describes a case of haematuria during attacks of malaria, which may have been due to malarial nephritis.

KOPP and SOLOMON (p. 582) have studied the effect of malaria on the liver in patients inoculated with *P. vivax* and in whom 4–12 paroxysms were experienced before treatment was given. Impairment of function occurred but was transient; function was fully restored 3–6 weeks after the malaria was terminated.

RICE and WATSON (p. 819) note that in the Tennessee Valley there is little or no correlation between malaria morbidity and the presence of parasites in the blood.

WILCOX (p. 432) has prepared a manual for the microscopical diagnosis of malaria in man. The Medical Department, Sierra Leone (p. 432), has described a modification of Field's method of staining.

DULANEY *et al.* (p. 11) have carried further their work on the complement fixation test in malaria, in which an antigen prepared from *P. knowlesi* is used. The test was positive in 81·6 per cent. of patients in whose blood malaria parasites were present; and in 88 per cent. of 317 patients (177 of whom were proved not to be suffering from malaria, the remainder being malarial) there was agreement between the test and the blood findings. Sera from patients with leprosy, amoebic dysentery and Chagas's disease gave a high proportion of positive results. The conclusion is that the test is highly specific and may be useful to supplement blood examination in the diagnosis of malaria.

NIYOGI (p. 750) describes the antigen from *P. knowlesi* used in the complement fixation test for human malaria; the test is positive in *P. vivax* infections.

HARMSEN and HAUER (p. 669) report on the Wassermann, Kahn and Meinicke tests in benign tertian malaria in patients free from clinical signs of syphilis. Fresh infections gave positive results in up to 90 per cent. of patients tested after the fourth or fifth paroxysm; the Kahn gave most positive results. The serum remains positive for some time after parasites have disappeared from the blood. In all, more than half of 1,000 tests were positive. DE GROAT (p. 820) has applied the various Kahn tests to the sera of 18 patients with malaria, but clinically free from syphilis. Seven were positive to the Standard, 10 to the Presumptive and 14 to the Verification (general biologic type). Those positive to the Standard test became negative in 1–3 months. The Verification test persisted longer, but eventually became negative in all cases except one. *Charles Wilcocks.*

[*To be continued.*]

RABIES.

A REVIEW OF RECENT ARTICLES. XL.*

i. *Virus.*

DE OLIVEIRA[1] has produced a tome of some 120 pages which gives a detailed account of his painstaking observations on different methods of propagating the virus of rabies in cultures. The article is divided into five chapters. In the first, reference is made to the strains of virus employed in these experiments. One of these was a fixed strain which on 27.9.1941 had been passaged 2,013 times by the intracerebral route in rabbits, the other was a street strain recovered from a rabid dog. The fixed strain (Lisbon) is undergoing some modification in that the incubation and duration of the disease are now shorter in the inoculated rabbits and the virus appears to be more sensitive to the action of glycerin and "desiccation" than in earlier passages. The second chapter deals with experiments made to propagate the virus in tissue cultures. [LEVADITI in 1914 showed that it was possible to cultivate the virus in nerve ganglia implanted in monkey plasma. STOEL in 1930 succeeded in propagating the virus in the brain of rabbit embryos in rabbit plasma and also, although less satisfactorily, in the heart of chick embryos in rabbit plasma. KANAZAWA in 1936 and 1937 cultivated the virus of rabies in the brains of rabbit embryos suspended in a liquid phase (Tyrode's solution). PLOTZ and REAGAN [this *Bulletin* 1942, v. 39, 589] cultivated street virus in chick-embryo brain tissue in monkey-serum-Tyrode's solution]. The present author has employed a method similar to that of WEBSTER and CLOW [this *Bulletin*, 1938, v. 35, 168] [see also SCHULTZ and WILLIAMS (this *Bulletin*, 1938, v. 35, 641)] whose medium consisted of a thick suspension of the brain tissue

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* For the thirty-ninth of this series see this *Bulletin*, v. 40, p. 651.

[1] DE OLIVEIRA, J. C. Sôbre o virus rábica e seus métodos de cultura. *Arquivos Inst. Bact. Câmara Pestana.* 1942, v. 8, 11–131, 25 figs. (1 coloured) on 13 pls. [Bibliography.] English summary 110–15.

of mouse embryos in Tyrode's solution with 10 per cent. monkey serum added, and who made 42 passages of mouse brain virus in such cultures. In addition to monkey serum he tried human, rabbit, donkey and guineapig serum ; these last three sera gave unsatisfactory results, the virus died out on the second passage when donkey serum was used, and rabbit and guineapig serum gave negative results. Eight passages were made in the medium with human serum. There was no indication that the virus content of such cultures was high enough to justify them as a source of virus for vaccine production and this agrees with the final observation of the American workers [see WEBSTER and CASALS, this *Bulletin*, 1942, v. 39, 82].

The third chapter records the first attempts to repeat PERAGALLO's experiments [this *Bulletin*, 1938, v. 35, 168]. That author, employing developing chick-embryos in eggs which had been incubated for 14 to 15 days, and rabbit brain virus, claims to have cultivated the virus of rabies in the chorio-allantoic membrane. He also published drawings of Negri bodies in the epithelium of the infected membranes. The present author employed a simple technique (no removal of a window and production of an artificial air sac as in Burnet's method) to inoculate the chorio-allantoic membrane of 10- to 17-day incubated developing chick embryos. The eggs, after inoculation with either street or fixed virus, were incubated at 38·5°C., later at 36 to 37°C., and the eggs were opened from the fourth to the sixth day. Nine series of inoculations were made, eight with fixed virus and one with street virus, and a large number of eggs were used with negative results, except in one instance in which the chorio-allantoic membrane of a 13-day egg in the first passage of the fixed virus proved infective for a rabbit.

In the fourth chapter a description is given, and this is illustrated by 25 figures on 13 plates, of lesions observed in the chorio-allantoic membranes of developing chick embryos inoculated by the Burnet method with rabies virus, suspensions of normal rabbit and mouse brain, broth, powdered glass, physiological saline, suspensions of normal chorio-allantoic membranes, animal sera, etc. [The non-specific lesions figured and recorded are similar to those observed by BURNET, F. M. (Medical Research Council, Special Report Series No. 220, 1936), BURNET, F. M. & GALLOWAY, I. A. (*Brit. J. Exper. Path.*, 1934, v. 15, 105) ; GOLDSWORTHY, N. E. & MOPPETT, W. (*J. Path. & Bact.*, 1935, v. 41, 529 ; D'AUNOY, R. & EVANS, F. L. (*Jl. Path. & Bact.*, 1937, v. 44, 369).]

In the chorio-allantoic membranes inoculated with rabies virus all these non-specific lesions may be found and some of the membranes of younger embryos, although they were found to be infected with virus by rabbit or mouse inoculations, showed no lesions. The only lesion recorded in some eggs inoculated with rabies virus, which was not seen in the other inoculated eggs referred to above, was an infiltration with spongioblasts, but this was not constant and its significance was not determined. The general conclusion is that the rabies virus produced no specific lesions in the chorio-allantoic membrane and in none of the inoculated embryos (4 to 14 days old) were Negri bodies found in the membrane. Attempts were made to increase the receptivity of the membranes for rabies virus, and these and experiments with younger developing chick embryos are described in the fifth chapter. BURNET's technique was employed but no success was attained with 10- to 14-day-old eggs even when the inoculated

virus was suspended in Tyrode's solution and diluted serum instead of in physiological saline. Graded doses of X-rays were applied to the chorio-allantoic membranes (10- to 13-day-old embryos) prior to inoculation with rabies virus, but although the membranes of the first and second passage were infective for rabbits subsequent passages gave negative results. One per cent. ascorbic acid had no deleterious action on the virus but its presence in the inoculum did not affect the non-survival of the virus in the chorio-allantoic membranes of 10- to 14-day-old embryos. Finally KLIGLER and BERNKOPF's [this *Bulletin*, 1939, v. 36, 724] results were confirmed. It was found possible to propagate the virus in 4- to 5-day-old embryos, the eggs being opened on the 9th to 10th day after inoculation, for passage. Virus was detected by mouse inoculation in the chorio-allantoic membranes and brains of the embryos of inoculated eggs up to the ninth passage and the experiments were not continued. However, while a detailed estimate of the virus content of the inoculated chorio-allantoic membranes was not made, it was found that a suspension of the membrane of the ninth passage had a titre of only 10^{-2} and this was equivalent to the virus titre of the eight passage tissue culture referred to in the second chapter. Mouse brains were shown to have a virus titre of at least 10^{-5} and rabbit brains sometimes showed a similar virus content. With regard to tissue cultures reference is made to the possibility of accidental contamination by the virus of lymphocytic choriomeningitis. [Such contamination of cultures has been recorded by CASALS-ARIET and WEBSTER, this *Bulletin*, 1940, v. 37, 622.]

SIGURDSSON[2] has emphasized that virus material to be used for the preparation of rabies vaccine should contain virus in high concentration, be free of contaminating viruses and bacteria and be as easily prepared and inexpensive as possible. Up to the present, tissue cultures and chick embryos have been found poorer in virus than animal brain tissues. His paper reports attempts to increase the yield of rabies virus in the chick embryo. The author used two strains of fixed virus, one " the old Pasteur strain " which had had a very large number of mouse brain passages, and the other was " strain 15811 " which had been passaged 114 times in mice ; it was fixed in virulence but it was more invasive than the " old Pasteur strain." Preliminary experiments were made by inoculating virus on to the chorio-allantoic membranes and these showed that " strain 15811 " reached the embryo brain more easily than the Pasteur strain. The former strain was used for subsequent experiments. Virus was inoculated intracerebrally into 8-day old chick embryos and the virus content of pooled embryo brains was estimated after incubation of the eggs at 35°C. to 36°C. for different lengths of time. " The virus reached a titre of $10^{-5.5}$ to $10^{-6.5}$ in five to six days." The author is of the opinion that these virus titres, which are somewhat higher than those recorded by other workers and than those in the case of eggs incubated at temperatures of 39°C. to 40°C., may be due to the lower temperature of incubation. It is stated that the observations of KLIGLER and BERNKOPF [this *Bulletin*, 1939, v. 36, 724, ; 1941, v. 38, 494] and of DAWSON [this *Bulletin*, 1942, v. 39, 80] have been generally confirmed. [Two points are worthy of mention with regard to Dawson's experiments on inoculation of rabies virus directly into the chick embryo brain. He showed that

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SIGURDSSON, B. The Yield of Rabies Virus in the Chick Embryo. *J. Exper. Med.* 1943, Nov. 1, v. 78, No. 5, 341–5, 1 fig. [10 refs.]

in later passages it was found that infection could be produced by injection on the chorio-allantoic membrane, into the muscles of the thigh of the embryo and the yolk sac, which indicated some adaptation to the chick embryo. Furthermore, he found that with one strain of virus, chick embryo brain passage led to marked reduction in pathogenicity for rabbit and mouse with production of a mild disease which immunized the inoculated animals. BERNKOPF and KLIGLER [this *Bulletin*, 1942, v. 39, 79] also reported a lessened pathogenicity of chick embryo-passaged virus for the rabbit. It might not, therefore, follow that one could always correlate the antigenic potency of a vaccine with the virus potency of the material from which it was made, as the results might be governed by the animal used for test]. BERNKOPF and NACHTIGAL[3] have developed a new method of carrying out complement fixation tests in rabies. CASALS and PALACIOS [*J. Exper. Med.*, 1941, v. 74, 409–426] described a method which they found to be satisfactory for virus infections of the central nervous system. The present authors found their procedure for preparing antigen complicated and they considered it desirable to develop a simpler technique for complement fixation "which might find application in routine laboratory diagnosis." At first they obtained good results with Miss HOWITT's method of preparing antigen [HOWITT, *J. Immunol.*, 1937, v. 33, 235], but they thought that further simplification was possible. [CASALS and PALACIOS, incidentally, have reported unfavourable results with Howitt's method of preparing antigen.] Several other workers have reported contradictory results with rabies virus. [GREVAL, *Indian J. Med. Res.*, 1933, v. 20, 913; and HAVENS and MAYFIELD, *J. Infect. Dis.*, 1932, v. 50, 367, using sheep and guineapig hyperimmune sera respectively, reported positive complement fixation in rabies.]

The antigen of Bernkopf and Nachtigal was prepared by taking 1 to 2 gm. of rabies-infected brain material, mincing it in a Petri dish, spreading it in a thin layer, and drying it in a desiccator over H_2SO_4 at 37°C. for 24 hours. Preliminary drying is stated to be important since antigen prepared from fresh undried material was found to be anticomplementary. The dried virus material is scraped off and stored in rubber-stoppered tubes in an ice box and it will keep for nine months. For use, the antigen is taken up after grinding in a mortar in physiological saline to give a 2 per cent. suspension, it is centrifuged for 15 minutes at 3,000 r.p.m. This type of antigen has been prepared from the brains of rabbits, guineapigs, mice and dogs infected with mouse-passaged virus, virus from tissue cultures, egg-passaged virus, and local strains of street virus. Controls have included antigens prepared from the brains of guineapigs and mice infected with equine encephalomyelitis, the brains of guineapigs infected with murine typhus and normal brains of mice, guineapigs, rabbits and dogs. The sera used were those of hyperimmunized guineapigs which had been injected with a 10 per cent. suspension of homologous rabies brain vaccine containing 1 per cent. formalin. Three courses of immunization were given, each consisting of four injections of 5 cc. with a four-day interval. One group of guineapigs was immunized with a living culture virus and with a formalin-inactivated strain of street virus. The sera were heated to 56°C. for 30 minutes. The mixtures were left for 16 to 18 hours in the ice box and then at 18°C. to 20°C. for complement fixation. Water

[3] BERNKOPF, H. & NACHTIGAL, D. Complement Fixation Test with Sera of Animals immunized with Rabies Virus. *Proc. Soc. Exper. Biol. & Med.* 1943, May, v. 53, No. 1, 36–8.

bath fixation at 37°C. was not sufficiently sensitive. After addition of the haemolytic system the mixtures were incubated for 30 minutes at 37°C. The results showed that the anti-rabies immune sera gave specific fixation and failed to react with brain antigens from animals infected with typhus or equine encephalomyelitis or with normal brain antigens. Antisera, produced by immunization with a local strain of street virus, fixed complement in lower titres than did sera of animals immunized with fixed virus when either fixed virus or street virus antigens were employed. The latter sera gave a positive reaction up to 1 : 400 with standard antigens prepared from the brain of mice infected with fixed virus. When the brains of dogs infected with the author's strain of street virus were employed to prepare the antigens it was found that sera with a maximum titre of 1 : 125 failed to react with the antigen, whereas positive results were obtained with the antigen only when sera of a titre of at least 1 : 250 were employed. This may be due to the lower virus titre of dog brains as compared with, say, mouse brains. When different parts of the virus-infected dog brains were tested for their antigen content considerable differences were observed. The highest titre was always recorded in the medulla. This technique for preparing the rabies antigen for complement fixation was not satisfactory for the preparation of antigen in the case of equine-encephalomyelitis as the antigen appears to be destroyed. It is interesting to note that frozen brain material dried *in vacuo* exhibited marked anticomplementary action. The complement-fixing antibodies reached their maximum titre in about one week after the last vaccine injection, decreased to about one-eighth of the titre in one month and they were no longer detectable after four months. Virus-neutralizing antibodies on the other hand reached a maximum in one month and were still present after four months. [The results recorded by BERNKOPF and NACHTIGAL, and CASALS and PALACIOS with rabies virus are interesting and promising but it would appear that confirmation and extension of their observations are necessary before complement fixation can be said to be available for "routine laboratory diagnosis."]

ii. *Symptoms and Diagnosis.*

The virus infectivity of the saliva of rabid animals was demonstrated in the early part of last century. It is known that excessive salivation is a characteristic feature of rabies in man and PASTEUR, CHAMBERLAND & ROUX and others demonstrated virus in the saliva of human beings with rabies in 1881 during the early basic studies of the disease. Within recent years PALAWANDOW & SEREBRENNAJA and PAWAN have demonstrated virus in saliva collected from patients infected with rabies by bites from rabid dogs or vampire bats.

The virus has been recovered from the parotid, submaxillary and sublingual glands by PASTEUR, CHAMBERLAND & ROUX and others. SULKIN and HARFORD[4] report the recovery of the virus of rabies from the saliva of a human patient bitten by a stray dog. The dog was shot and numerous Negri bodies were demonstrated in the *cornu ammonis*. Thirteen persons in all were bitten by this dog, and of these, eleven, in addition to having their wounds cauterized with carbolic acid shortly after exposure to infection, received vaccine treatment (Harris vaccine). [In this method of preparing vaccine, which has not come

[4] SULKIN, S. E. & HARFORD, C. G. Concerning the Infectivity of Saliva in Human Rabies. *Ann. Intern. Med.* 1943, Aug., v. 19, No. 2, 256–62. [19 refs.]

into use on a large scale, the cords and brains of rabies-infected rabbits are frozen with carbon dioxide snow, ground up finely while frozen, and the material is then dried over sulphuric acid *in vacuo* at −18°C. ; this treatment is said to produce a 50 per cent. reduction in virus infectivity.] Of the eleven patients who underwent treatment, two died of rabies ; a patient who had refused treatment also died of rabies. A specimen of saliva was collected from one of the patients who had received treatment but who subsequently died of rabies (numerous Negri bodies were found in the *cornu ammonis* on autopsy) ; the saliva, which was ropy and coagulated in the tube, was collected 22 days after exposure to infection and within the 24 hours preceding death during a convulsive seizure, when salivation was very profuse. This specimen was proved to contain the virus of rabies by the intracerebral inoculation of mice.

Another sample of virus was collected from the patient who died of rabies (numerous Negri bodies in the *cornu ammonis* on autopsy) after refusing treatment. This saliva was collected about 10 hours before death and 40 days after exposure to infection, by swabbing the mouth and throat, while the patient was under the influence of a powerful sedative, and no virus was demonstrated therein. It is suggested that failure to recover virus from the saliva of rabid human patients reported in the literature may, as in the present case, have been due to collection at a time when there was no copious flow such as is coincident with a convulsion.

Points of interest about the recovery of the virus from the saliva are that mice were used and groups of these were inoculated intracerebrally with either untreated or ether-treated material. It is known that several viruses, including those of poliomyelitis, influenza, foot-and-mouth disease and rabies, will resist treatment with ether. In the present instance this agent was employed to eliminate bacteria from the heavily contaminated saliva (shaking with 10 per cent. ether and allowing to stand in a refrigerator for 2 hours with subsequent centrifugation, removal and discarding of the supernatant ether layer). However, some of the group of mice inoculated with the untreated saliva developed rabies in the same way as mice of the group inoculated with the ether-treated material, Negri bodies being demonstrated in the brains of some of the inoculated mice and transmissible virus being recovered from others. Thus the contaminating micro-organisms did not kill the mice, indicating that they were not pathogenic for that species. [This confirms the observations of other investigators that mice inoculated intracerebrally with material infected with bacteria are less likely to succumb to their effects, before the virus can take effect, than guineapigs and rabbits.]

In addition the virus recovered from the saliva was passaged twice in mice and then serum neutralization tests were carried out by inoculating groups of 15 mice with mixtures of a 1 : 1,000 dilution of a 20 per cent. suspension of the virus in beef infusion broth containing 20 per cent. normal horse serum with the following sera : A. Serum, from the patient who did not receive vaccine treatment, collected 39 days after exposure to infection and shortly before death from rabies ; B. Serum of a patient who received vaccine treatment, collected 20 days after the bite and 11 days after the completion of the course of injections ; C. Pooled serum from two rabbits hyperimmunized with the strain of fixed virus employed for preparing the vaccine ; and D. Normal human serum. A and D showed no virus-neutralizing properties, while B and C did.

In conclusion as the saliva of human beings may contain rabies virus, it is wise when attending to rabid patients, to take reasonable precautions to prevent saliva from coming in contact with wounds, abrasions or the mucous membranes of attendants.

iii. *Pathology.*

PASTEUR and his collaborators and numerous other workers have shown that in street rabies, as in experimental rabies, the whole cerebrospinal axis is infected with virus, and the nerves, especially those of the limbs, while they are infective, are less so and in some cases, depending on circumstances, are even free from virus. The sympathetic nervous system has probably received less attention than it merits in this connexion. However, the ramifications of the sympathetic nerves are widespread and since, as has been shown by MANOUÉLIAN[5] in previous studies, the neurones of the sympathetic nervous system are infected with virus, it is not difficult to understand why the portions of organs and viscera containing them are infective also. The author here points out that it is easy, especially in big dogs, to isolate the nerve filaments of the sympathetic nervous system, which can be examined histologically for lesions and also be tested for virus infectivity. It has been shown that in the dog infected with street virus there exist in the nerve filaments of the solar plexus definite lesions of the endoneurocytes. These consist of chromatolysis, fusion of the neurofibrils into "cordons" ("twist"), nuclear changes, destruction and disappearance of the cytoplasm and nucleus with replacement by a nodule of cells of neoformation. Negri bodies can be demonstrated in the cytoplasm of the endoneurocytes. A diagnosis of rabies can be made by histological examination of the nerve filaments of the sympathetic nervous system and inoculation of suspensions of the nerve filaments into susceptible animals. In three experiments the presence of virus in the nerve filaments of the solar plexus was demonstrated by inoculation of rabbits intracerebrally. These animals developed rabies in 12–14 days and characteristic lesions of the disease were demonstrated at post-mortem.

iv. *Methods of Treatment and Statistics.*

Prevention of rabies by local treatment of the bites inflicted by rabid animals has occupied the attention of physicians from at least as early as the 1st century A.D. CELSUS, DIOSCORIDUS and GALEN advised cauterization with a hot iron and GALEN in addition suggested incision and maintenance of a running ulcer for at least 40 days. Many other methods of cautery have been tried since. In addition to gunpowder, which was inserted into the wounds and set alight, nitric acid and silver nitrate mentioned by SHAUGHNESSY and ZICHIS[6], sulphuric acid, hydrochloric acid, caustic potash, antimony chloride and corrosive sublimate have been used. Cautery was carried out even on face and neck wounds and its dreadful effects probably deterred many physicians from applying it.

BABES in 1894 [*Ann. Inst. Pasteur*, v. 8, 434] studied the effect of thermocautery on wounds in dogs and rabbits contaminated with

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[5] MANOUÉLIAN, Y. Démonstration expérimentale de la virulence rabique des filets du plexus solaire et des endoneurocytes. *Ann. Inst. Pasteur.* 1942, Nov.–Dec., v. 68, Nos. 11–12, 550–52, 2 figs.

[6] SHAUGHNESSY, H. J. & ZICHIS, J. Prevention of Experimental Rabies. Treatment of Wounds contaminated by Rabies Virus with Fuming Nitric Acid, Soap Solution, Sulfanilamide or Tincture of Iodine. *J. Amer. Med. Ass.* 1943, Oct. 30, v. 123, No. 9, 528–33. [Refs. in footnotes.]

fixed rabies virus. The number of animals involved in this experiment was small but it appeared that cauterization by this means, if applied 25 minutes after infection, had little or no effect in arresting the development of the disease. In the opinion of the present authors the published clinical and experimental evidence was insufficient to establish the value of the cauterization of bites by fuming nitric acid in the prevention of rabies, yet apparently in America most public health and medical authorities recommend that bites be treated with nitric acid.

Reference is made to the early experiments of CABOT [*Medical News*, 1899, v. 74, 329] and POOR, 1911 [*Collected Studies from the Research Laboratory, No. 6, Dept. of Health, New York*], and the remarks of ROSENAU [*Preventive Medicine and Hygiene*, 1935, 6th ed., Appleton-Century Co., New York, p. 353]; and it is pointed out that it is on the basis of this evidence, which is not fully convincing, that the method has come into vogue. Cauterization with fuming nitric acid produces many undesirable effects; it is painful, has a destructive action on the tissues leading to bacterial infection, and healing is usually slow. Physicians are loathe to apply nitric acid if the wounds are deep and lacerated and on the face since contractions may result and damage to the periosteal and bony tissues may ensue. The authors decided to investigate more thoroughly the effects of nitric acid, irrigation with soap solution, treatment with tincture of iodine and packing with sulphanilamide on wounds infected with rabies virus. It was decided that in these experiments guineapigs and mice should be infected with rabies virus in a manner that would approach very closely the common mode of infection by the bite of the rabid animal. A search was made for a strain of street virus which would infect regularly by the subcutaneous or intramuscular route. Twenty-eight strains were examined and only five of these produced rabies in about 50 per cent. of mice and guineapigs by these routes in first passages. These strains were used only in preliminary experiments. Preference was given to strain S1, a fixed rabies strain, which it was found consistently infected mice and guineapigs by the intramuscular route. Mice were later discarded as unsuitable for these experiments, as in preliminary trials many died from the ill effects of treatment applied.

Eighteen experiments were carried out on 594 guineapigs which were treated, and there were 279 untreated control guineapigs. Guineapigs of 300 to 450 gm. were employed and they were kept under observation for 35 days and in some cases up to a year. Two methods of infecting the wounds with virus were employed. Wounds 12 mm. long and 6 mm. deep were made in the muscles at the back of the neck and these were infected with virus, irritation of the wound being carried out with an injection needle, or virus was injected into these muscles to a depth of 3 mm. and then wounds 12 mm. long and 6 mm. deep were made. Nitric acid was applied with a glass rod, 20 per cent. green soap solution by syringing with a hypodermic syringe (through a hole in the bottom of a beaker placed over wound to avoid risk to the operator). Iodine was applied with a cotton swab on a small stick.

The wounds treated with nitric acid developed severe burning and scarring and they took 28 days to heal. Soap solution and iodine had no harmful effects. It should be remembered, however, that tincture of iodine causes discomfort if applied to open wounds and in some instances chemical burns (if it be not freshly made, owing to the formation of hydriodic acid).

The treatment of the wounds was carried out on three groups of guineapigs 30 minutes, 2 hours and 6 hours respectively after virus infection. The results may be summarized in the following Table :—

	Group 1 30 minutes	Group 2 2 hours	Group 3 6 hours
Nitric acid	65/75	65/80	38/60
Soap	67/75	68/80	40/60
Iodine...	54/60	12/20	—
Controls	29/75	22/80	31/60

Numerator represents survivors of infection with rabies.
Denominator represents number of guineapigs employed.

N.B.—The results recorded here for Group 3 are those of Table 3 in the text of the paper—there is an error in the total of controls given in the latter, *viz.*, 41/60 instead of 31/60.

The authors conclude from these results that while cauterization with fuming nitric acid has a definite value in preventing the development of rabies, irrigation with 20 per cent. soap solution is just as effective. They state that the results indicated that a slightly better effect was obtained when treatment was applied 30 minutes after infection than after 2 hours, and that after 6 hours the effect was less still, in the cases in which nitric acid and soap solution were employed. (However, there would appear to be no appreciable statistical difference between the results after 2 hours and after 30 minutes and it is extremely doubtful whether there was any effect after 6 hours.)

It is also stated that since iodine was less effective after 2 hours than after 30 minutes no test was made after 6 hours [the number of guineapigs employed in the 2 hours test was, however, small].

It is stressed that since it is a matter of considerable difficulty to apply satisfactory local treatment, especially to deep or punctured wounds, vaccination treatment should be given in addition. Sulphanilamide treatment had no effect in preventing the development of rabies in treated guineapigs.

Since it has been demonstrated that biological products such as therapeutic sera may become contaminated with anaerobic bacteria even if they contain antiseptics, ZEUNER[7] has undertaken an investigation on the effect of antiseptics such as are generally used in rabies vaccines, formalin, carbolic acid and ether, in preventing the growth of sporulating and non-sporulating bacteria added to rabies vaccines in which these bactericidal substances are employed such as those of HEMPT (ether and phenol), SEMPLE (phenol) and VAN STOCKUM (formalin). It seemed advisable to make these studies since rabies vaccines have higher lipoid and protein concentration than some other biological products and accidental contamination of such vaccines might occur, especially in those circumstances in which there is decentralization of rabies services, with less perfect laboratory conditions; and vaccines may be stored in bulk for some time before distribution into phials for issue, and bacterial contamination may occur during transfer.

[7] ZEUNER, H. Untersuchungen ueber die Fähigkeit der Selbststerilisierung bei Wutschutzimpfstoffen. *Zent. f. Bakt.* I. Abt. Orig. 1943, Jan. 20, v. 149, No. 7/8, 429–33.

Staphylococci (*aureus* and *albus*), *Bact. enteritidis* (Gärtner), *B. subtilis*, *Bact. coli*, the bacillus of malignant oedema and soil bacteria were used in these experiments as contaminating micro-organisms. The results showed that in the case of Semple's vaccine the phenol killed the sporeless bacteria and inhibited the growth of *B. subtilis*, while the vaccine was being incubated at 37°C. for 24 to 48 hours. In the case of contamination of the prepared vaccine, bacteria without spores were killed straight away, and although spores were not killed there was a suppression of their multiplication. The bactericidal effect of the VAN STOCKUM vaccine (formalin) surpassed at 37°C. that of the SEMPLE vaccine (phenol). However, after incubation there was a loss of formalin, which is a fact of importance as the possibility of subsequent bacterial contamination during manipulation of the vaccine is greater. Non-sporulating bacteria are destroyed rapidly in the Hempt vaccine in spite of its higher lipoid and protein content, but this is not the case with the spore bearers.

Pasteur employed the dried spinal cords of rabbits in the preparation of the first rabies vaccine. Since then other vaccines have been devised and in their preparation spinal cords or spinal cords and brains have been employed. More recently the relationship between the original virus content of the material from which a vaccine is made and its antigenic potency or immunizing value has been demonstrated by WEBSTER [this *Bulletin*, 1940, v. 37, 194 and 619] and HABEL [this *Bulletin*, 1941, v. 38, 495].

Comparisons of the virus content of the brains and spinal cords of animals infected with rabies have not been recorded extensively. HABEL reported in observations on three rabbits that the brains titred 10^{-4}, 10^{-4} and 10^{-4} and the cords 10^{-3}, 10^{-4} and 10^{-3}. LÉPINE [this *Bulletin*, 1938, v. 35, 642] drew attention to the progressive decrease in the virus-infectivity of the spinal cord and the increase of that of the brain of infected rabbits as a result of continued intracerebral passage of the Pasteur (Paris) fixed strain over many years.

DUNLAP[8] has undertaken experiments to determine differences in the virus content of the brain and spinal cords of sheep which were prostrate after intracerebral infection with rabies fixed virus and to determine the immunizing value of vaccines prepared from these two sources. The samples of brain and spinal cord tissue were collected from sheep showing typical symptoms of rabies following intracerebral inoculation with rabies fixed virus (Pasteur strain). The material was collected on the 6th or 7th day after inoculation. The samples of brain tissue consisted of 1 to 2 gm. removed from the cerebrum near the longitudinal fissure of the uninoculated side. The spinal cord samples consisted of 1 gm. each taken from the middle of the cervical and the middle of the thoracic regions respectively. 10 per cent. fine suspensions of the tissues were made by grinding in a pyrex glass grinder. The fluids for dilutions were saline for guineapig inoculations and distilled water plus 10 per cent. serum (MILAM) for the inoculation of the mice with higher dilutions. The intracerebral inoculations were made as quickly as possible after making dilutions. The experimental animals were observed for three weeks, and death and survivals were recorded. The method used for determining the limiting infective dilutions or end points was that of REED and MUENCH [*Amer. J. Hyg.* 1938, v. 27, 493]. It was realized that the method of collecting

[8] DUNLAP, G. L. Comparative Value of Brains and Cords of Sheep in Rabies Vaccine. *J. Amer. Vet. Med. Ass.* 1943, July, v. 103, No. 796, 11–14.

the tissue samples may not have been ideal especially as LEACH and JOHNSON reported higher concentrations of virus in some regions of the brain of humans as compared with others [this *Bulletin*, 1940, v. 37, 616]. It was found that there were considerable variations in the titre of the spinal cords and brains from different sheep, 1 : 400 to 1 : 30,000 for the cords and 10^{-5} to 10^{-7} for brains. [HABEL examined the virus content of the brains of 23 rabbits, two had a titre of 10^{-6} three 10^{-5}, thirteen 10^{-4} and five 10^{-3}.] This suggests the advisability of mixing the tissues from a number of rabies-infected animals in preparing vaccines. HABEL (*vide supra*) doubted whether spinal cords should be included in the material for making vaccines. COVELL, MCGUIRE, STEPHENS and LAHIRI [*Indian J. Med. Res.*, 1936, v. 24, 373] reported that vaccines made from the spinal cords of sheep were poor compared with those made from brain tissue. The present author made 40 per cent. tissue suspensions in 1 per cent. phenol and these were left at 70° to 74°F. for three weeks, then equal parts of saline and suspension were mixed. These diluted suspensions constituted the vaccines and they proved non-infective for rabbits by intracerebral inoculation. They were stored at 40°F. for six months and were then tested by the "mouse potency test" [HABEL, this *Bulletin*, 1941, v. 38, 161]. Some irregularities were observed but the brain vaccines were always superior to the cord vaccines, which were consistently very poor. It is stressed that while the mouse test is a useful one, the application of too strict mathematical interpretations to biological problems has weaknesses, thus the loss or survival of a mouse may make a difference of 100,000 m.l.d. or greater in the result of a potency test as calculated by the Reed and Muench method. Spinal cord vaccines were of little or no protective value after storage for six months. The results confirm the observations on the direct relationship between the original virus content of the material from which vaccines are made and their immunizing value, and strongly suggest the advisability of always testing the potency of virus material used for this purpose.

CLEMENTE[9] records the results of vaccine treatment by the Högyes method carried out in the rabies service of the National Institute of Health, Madrid, during the years 1939–41 ; 1,296 patients were treated in 1939, 1,150 in 1940, and 1,276 in 1941, and there was one fatal case in 1941, a mortality rate for that year of 0·078 per cent. or a mortality rate for the three years of 0·0269 per cent. The records for 1928 to 1938 were not available owing to the civil war. The figures for 1901 to 1927, which were published previously by J. RAMON Y FAÑANÁS [*Arch. Inst. Nacional Hig. Alf. XIII*, 1929–30, v. 6 and 7, No. 6, p. 45] were 15,065 cases treated and 17 deaths, a mortality rate of 0·11 per cent., but five of these deaths occurred in 1901. In very serious cases of rabies in addition to the special dosage for severe disease for the first ten days, it has been customary to inject 5 cc. of a Semple vaccine also. The author states that he personally has observed only a few cases of post-vaccinal paralysis and all were benign, short in duration and followed by complete recovery. He was aware that serious cases of transverse myelitis have occurred as a result of the vaccine treatment but the remarks on the question are diffuse and conspicuous by their vagueness.

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[9] CLEMENTE, P. Tratamiento antirrábico. Método de Högyes. Sus fundamentos y sus ventajas. Resultados obtenidos. Nuestra estadistica. Reprinted from *Rev. Sanidad e Hig. Pública.* 1943, May–June, v. 17, No. 3, 20 pp.

CECCALDI[10] reports that at the Pasteur Institute of Brazzaville the Semple method of preparing rabies vaccine has been adopted since it allows of decentralization of the service. A 1 per cent. brain suspension is used and 0·5 per cent. carbolic acid. The mixture is left for 24 hours at 26°C. to 29°C. (laboratory temperature) or in an incubator at 28°C. for the same time, and the vaccine is then stored for from five to seven days in the ice chest before use. It is stated that the vaccine will maintain its efficiency for three months if stored in an ice chest, but no mention is made of how this conclusion was reached ; 15 injections are given in daily doses and in serious cases 20 injections. In the case of face bites two injections of 5 cc. are given per day for the first three days. Forty-seven cases were treated during the year but there was a complete medical history in only 24 of these and there were two deaths from rabies. The first death occurred four days after the bite of the rabid dog (bitten by a hyena) and the second 10 days after the bite. In four cases the bites were about the head and face and in the other 20 cases on the extremities. Two strains of fixed virus are now being maintained, one is the Pasteur (Paris) strain and the other is referred to as the Brazzaville " jeune chien " strain.

CRUVEILHIER and VIALA[11] report that during the year 1942, 588 persons presented themselves for treatment with vaccine at the Pasteur Institute Paris ; in 214 of these treatment was considered necessary ; 153 had been bitten by dogs, 49 by cats, and 12 by rats. Two hundred and thirteen belonged to Category C and one to Category A. There were 185 deep bites and 29 superficial ; 136 were bites without the interposition of clothing. There were 15 head bites, 130 of the upper limbs, 3 of the trunk, and 66 on the lower limbs ; 135 patients were treated within the first four days after infection, 54 between the 5th and 14th day, 16 between the 15th and 21st day and nine later than this. There were no deaths and no cases of post-vaccinal paralysis.

v. *Rabies in Animals.*

COCEANI[12] records experiments in which he has employed the brain tissue of calves infected with rabbit fixed virus for the preparation of a carbolized vaccine for dogs. KERBLER [this *Bulletin*, 1931, v. 28, 747] had already shown that fixed virus, recovered from sheep inoculated with rabbit fixed rabies virus, was satisfactory. JACOTOT and LE ROUX [this *Bulletin*, 1938, v. 35, 168] considered the use of horses and calves for the production of fixed virus material for vaccine preparation. They had found that a dog inoculated with rabbit fixed rabies virus yielded a quantity of virus material for the preparation of vaccine for dogs equivalent to that obtained from 8 to 10 rabbits. A pony of 300 kgm. yielded 500 gm. of virus material (nervous tissue) and a calf of 120 kgm. 350 gm., equivalent to the virus-infected nervous tissue of five to six dogs. Calves were preferred to horses because the symptoms were constantly paralytic, as distinct from those seen in horses in which excitation was observed on occasion. First-passage

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[10] BRAZZAVILLE [AFRIQUE FRANÇAISE LIBRE] : RAPPORT SUR LE FONCTIONNEMENT TECHNIQUE DE L'INSTITUT PASTEUR EN 1941 [CECCALDI, J., Director]. 21–6. Rage.

[11] CRUVEILHIER, L. & VIALA, C. Les vaccinations antirabiques à l'Institut Pasteur en 1941. *Ann. Inst. Pasteur.* 1942, Nov.–Dec., v. 68, No. 11–12, 545–7.

[12] COCEANI, A. Studio ed applicazione nella profilassi antirabbica del cane di un vaccino preparato con sostanza nervosa di vitello. *Boll. d. Soc. Italiana di Med. e. Igiene Trop.* (Sez. Eritrea.) Asmara. 1943, v. 2, No. 1, 38–44. English summary (6 lines).

virus material was considered to be better than that recovered in later passages, for vaccine preparation. Jacotot and Le Roux used 6 per cent. formalin to prepare this vaccine for immunity tests in guineapigs, but only a limited number of observations were made. The present author has found the calf to be satisfactory for the production of fixed rabies virus material (brain tissue) for the preparation of vaccine for use in dogs. The limiting infective dilution for rabbits by intracerebral inoculation of the suspension of brain tissue from an intracerebrally inoculated calf was stated to be 1 : 400,000. Carbolic acid was used instead of the formalin as employed in Jacotot and Le Roux' experiments. A 20 per cent. suspension of virus-infected brain tissue was used and 1 per cent. phenol in 50 per cent. glycerine. The preventive vaccine treatment of dogs consisted in giving three injections subcutaneously into the thigh of 5 cc. at six-day intervals. The first vaccine had been kept at 37°C. for 24 hours, the second vaccine at 22°C. for 24 hours and the third vaccine at 5°C. for the same period.

A test was made to determine the efficacy of the vaccine in protecting dogs against infection with street virus by the intramuscular route. It is stated that the result of this test " demonstrated clearly that the fixed rabbit virus passaged in the calf preserved a vaccinating power against street virus " and that this justified the production of the vaccine on a large scale. [In the tests, however, there were three vaccinated dogs and three untreated control dogs. None of the vaccinated dogs, when injected with street virus one month later, developed rabies, and of the controls one survived and two died of rabies. It has frequently been stressed in the literature on rabies vaccination, although it should be obvious, that such results have no statistical value and that groups of at least 20 to 30 dogs should be employed.] During 1941 and 1942, 2,000 dogs were vaccinated in the manner described and there were no ill effects from the vaccination except a few small local abscesses at the site of inoculation and four cases of paresis of the hindquarters. These latter are reported to have been cured by injections of strychnine. The only reason for the author's belief that the vaccine was satisfactory for protecting dogs in practice against rabies appears to be that there were many cases of rabies in dogs before vaccination was introduced, and there were no cases of rabies among the 2,000 vaccinated.

vi. *Miscellaneous.*

JOHNSON[13] has written an article on rabies. This is the second treatise on rabies which has emanated from America within the last two years. The other was by WEBSTER and it was reviewed a year ago [this *Bulletin*, 1943, v. 40, 269]. The method of approach to the subject has been different in each case and the present summary will no doubt appeal more strongly to the student of virus diseases than its predecessor, since it embodies more detailed information on the virus itself, on the general pathology of rabies and on the laboratory diagnosis of the disease. The treatise is somewhat longer than the pagination in the reference given here would suggest since in pages 630 (1) to 630 (17) such additional practical questions as " Laboratory Diagnosis of Rabies," " Prevention of Rabies after Exposure," " Reactions to Rabies Vaccine Treatment " and " Control of Rabies " are discussed. The summary of information should be very useful and while it is not

[13] JOHNSON, H. N. Rabies. Reprinted from *Oxford Loose-Leaf Medicine*. New York. 1943, Chap. xxvi, 599–630, 5 figs. (4 on coloured pls.) [Bibliography.]

by any means exhaustive there are few essential points to which some reference has not been made. The personal views of the author, while they may not all meet with general acceptance by experts on the subject, are not unduly forced and in most cases they are not widely at variance with current views on experimental facts and interpretations. However, there are many who would question his statement that the "rabies virus is not strictly neurotropic" and who would submit other explanations for the infectivity of the submaxillary glands and some other organs and tissues. BERTARELLI showed that if the nerve filaments to the submaxillary gland are sectioned during the incubative stages of rabies the glandular tissue does not become virulent, and the work of Manouélian and others would strongly suggest that the virus infectivity of the submaxillary gland and some other organs and viscera could be explained by the presence of the virus in the nerve ganglia, filaments and their endoneurocytes associated therewith. The histopathological changes in the submaxillary glands referred to by the present author as indicating "that the virus has a special affinity for the mucus-secreting cells" may be secondary effects to the nervous involvement. The author has failed apparently to recover the virus from the circulating blood, but on occasion other investigators have done so and the strain of virus and species of infected animal may be factors influencing the issue of such researches. Many physicians would no doubt question the advisability of the continued use of fuming nitric acid cauterization for the local treatment of bites as recommended by the author, and by most public health and medical authorities in America. It has many disadvantages, which are discussed in section iv of this Review of Recent Articles on Rabies. There is some evidence that thorough syringing with 20 per cent. green soap solution would be equally effective. [It is obvious that in the treatment of rabies in human beings it would be inhuman to suggest experimentation on a scale to produce sufficient statistical evidence as to the effects of the following :—(1) Non-treatment of bitten individuals. (2) Treatment of bitten persons by cautery or other local treatment. (3) Treatment by vaccination alone ; and (4) Treatment by methods (2) and (3) combined. In the present state of our knowledge it would be unwise to withhold vaccine treatment in those cases in which its use is most generally recommended and depend on the problematic effects of cauterization or other local treatment. Thorough irrigation of the wounds with soap solution might be a useful adjunct to vaccine treatment. The author's conclusion that since "there are records of large series of cases of exposure to rabid animal bite treated by incision and actual cautery or other local treatment with a very low mortality rate" . . . "too much reliance should not be placed on post exposure vaccine treatment" is surely neither logical nor justifiable.] For the demonstration of Negri bodies in the laboratory diagnosis of rabies the author, like many other American workers, favours impression preparations stained by Seller's method, first described in 1927 [*Amer. J. Pub. Health*, 1927, v. 17, 1080]. There are still, however, quite a number of technicians who place greater reliance on paraffin sections, and Mann's eosin-methylene blue stain ; the delay in diagnosis by use of the second method is insignificant.

The white mouse has become increasingly popular as a test animal in those cases in which a microscopical diagnosis has not been possible or has given an uncertain result and the present author has found it extremely useful.

There still appears to be a lack of efficient legislation in America for enforcing dog control and, as is pointed out here, this is very necessary and should be the responsibility of the Livestock Sanitary Association acting under the Federal Bureau of Animal Industry.

The American workers JOHNSON & LEACH and WEBSTER & CASALS, have shown that it is possible to give a reasonably good protection to dogs by vaccination with a relatively small dose of a non-infective preparation of fixed virus. "Vaccination of dogs no doubt can be a useful adjunct to the dog control regulations and might be made compulsory in infected areas but vaccinated dogs should not be allowed special privileges." *Ian A. Galloway.*

MALARIA.

WOLMAN, M. **Field's Stain.** [Correspondence.] *Trans. Roy. Soc. Trop. Med. & Hyg.* 1943, May, v. 36, No. 6, 363–4.

The author was often unable to obtain, with Field's stain [this *Bulletin*, 1942, v. 39, 17], the purple staining of the chromatin of malaria parasites, and found that the spirochaetes of relapsing fever were often understained and almost invisible. After experiments to find the best staining agents in the eosin and methylene-azur groups, he replaced eosin by erythrosin and azur I by methylene blue. His solutions are as follows :—

	Grammes		*Grammes*
Solution A—		Solution B—	
Unna's polychrome methylene blue ...	5·0	Erythrosin	1·0
Disodium hydrogen phosphate (anhydrous) ...	5·0	Disodium hydrogen phosphate (anhydrous) ...	5·0
Potassium dihydrogen phosphate (anhydrous)	6·25	Potassium dihydrogen phosphate (anhydrous)	6·25
Distilled water ...	500·0	Distilled water	500·0

"These solutions should be filtered and are then ready for immediate use.

"The technique of staining is: A blood drop, not too thick, freshly dried :—

1. Stained for 1 second in the A solution.
2. Rinsed in tap water for 2 to 3 seconds.
3. Stained for 1 second in B solution, and
4. Rinsed again and dried.

"This modified staining method has proved to be very satisfactory in our hands. The time of staining is about 5 seconds, and the Romanowsky effect with purple staining of the chromatin, as well as a clear blue staining of spirochaetes, when present, is invariably obtained."

Charles Wilcocks.

ANGELINI, G. Ueber die Anwesenheit von *Plasmodium falciparum* in Erythroblasten. [**The Presence of** *Plasmodium falciparum* **in Erythroblasts.**] *Deut. Tropenmed. Ztschr.* 1943, May 1, v. 47, No. 9, 226–8.

The question as to whether the parasites of malignant tertian malaria can invade immature red blood corpuscles, particularly the basophile normoblasts, which are devoid of any traces of haemoglobin, has

remained unanswered, in spite of the fact that certain observers claim to have seen parasites within normoblasts of one type or another. The author, who has examined sternal blood in cases of malarial infection, has not previously seen parasites within the normoblasts. In one case however, in which blood was withdrawn by puncture just at the moment of death from a very heavy infection, parasites were seen in normoblasts, but never in the basophile forms. In the heart blood fairly numerous normoblasts were present: 44 per cent. were polychromatic and 56 per cent. orthochromatic. Of the latter, 7 per cent. were infected with malarial parasites, while of the former very few were infected. In the bone marrow 8 per cent. of the normoblasts were basophile, 30 per cent. polychromatic and 62 per cent. orthochromatic. Of the polychromatic normoblasts 1 per cent. were infected, and of the orthochromatic 2 per cent. None of the basophile normoblasts was infected. The type of parasite present was the young ring or early developmental form. The author considers the invasion of immature red corpuscles by malarial parasites to be of rare occurrence, and then only in very heavy infections. *C. M. Wenyon.*

TOMMASO, P. Di un caso di terzana mista con due parasiti di *Plasmodium vivax* in una stessa amazia. [**A Case of Mixed Tertian Malaria with Two** *P. vivax* **Parasites in a Single Red Cell.**] *Boll. d. Soc. Italiana di Med. e Igiene Trop.* (Sez. Eritrea.) Asmara. 1943, v. 2, No. 1, 7–11. English summary (6 lines).

The author describes a case of mixed *P. falciparum* and *P. vivax* infection. In some of the red cells two *P. vivax* parasites were seen. A study of the appearances of the parasites in this dual infection of red cells led to the conclusion that direct binary fission of the parasite within the cell had taken place. *Norman White.*

DE MEILLON, B. **Remarks on the Entomology of Malaria in the Tropics and Sub-Tropics of Africa.** Reprinted from *Primeiro Congresso Méd. de Lourenço Marques.* 1938, Sept. 10, v. 3, 63–74.

The author has produced a compact, readable account of the entomologist's view of the malaria problem of Africa south of the Sahara. The paper is not one which can be further summarized. The author is altogether too modest in describing it as "remarks". *P. A. Buxton.*

RENN, C. E. **Emergent Vegetation, Mechanical Properties of the Water Surface, and Distribution of Anopheles Larvae.** *J. National Malaria Soc.* Tallahassee, Fla. 1943, v. 2, No. 1, 47–52, 3 figs.

The author discusses the distribution of Anopheles larvae among stems of aquatic grasses, and analyses the surface forces involved, by using simple mechanical models.

It is well known that larvae of *Anopheles quadrimaculatus*, and many other species, tend to be common among stems of aquatic grasses ("emergent vegetation") and rare in open water or where margins are clear. The emergent plants provide conditions which are to the advantage of the larvae for several reasons. The author limits himself to the study of surface forces; he does not consider to what extent the location of larvae may also depend on the place where the parent female deposited the eggs.

A simple mechanical model can be made from a large pan of water in which glass rods are set vertically. If the rods are waxed a depressed "negative meniscus" forms round them, like that round a grass stem which has not been long in water. If the rods are coated with agar the meniscus is raised, or "positive," as it is round a natural object which has become coated with microorganisms.

Among these rods, arranged in various patterns, larvae may be liberated. They tend to group themselves on positive menisci, with their tails close to the stems. Now it can easily be seen that the unwettable parts of the larva (palmate hairs, spiracular plate, etc.) are surrounded by negative menisci, but that there is a positive meniscus under the posterior edge of the spiracular plate, which is raised. Owing to surface forces this positive meniscus tends to draw the larva's tail towards the similar meniscus on the glass rods or stems of plants. This also can be demonstrated with small floating models. *P. A. Buxton.*

GOODWIN, M. H., Jr. & LENERT, L. G. **Methods used for investigating certain Hydrologic Problems related to Malaria.** *J. National Malaria Soc.* Tallahassee, Fla. 1943, v. 2, No. 1, 63–72, 5 figs. [21 refs.]

Discusses relation of breeding of *A. quadrimaculatus* in Georgia, U.S.A., to local geology.

HERMITTE, L. C. D. **Diagnosis of Pernicious Malaria.** [Correspondence.] *Trans. Roy. Soc. Trop. Med. & Hyg.* 1943, Sept., v. 37, No. 2, 166–7.

Hermitte, referring to the paper on pernicious malaria [this *Bulletin*, 1943, v. 40, 878], agrees with LINDSAY's views and thinks that they are valid for any place where *P. falciparum* is endemic, but questions the statement that the microscope has little place in the diagnosis of pernicious malaria. He advises the examination of films obtained by sternal or liver puncture as well as blood films; if all are negative subtertian malaria can be excluded, while malaria, in the presence of other disease, will not escape diagnosis. [Nevertheless, microscopical diagnosis depends on good staining technique. During military operations, facilities may not always be such that complete reliance can be placed upon examination of stained films. Clinical experience should not be rejected.] *J. F. Corson.*

WILCKENS, H. Frühlingsmalaria. Klinische Ueberlegungen zur Frage des Reticuloendothelstadiums der Malariaplasmodien. [**Spring Malaria. Clinical Reflections on the Question of the Reticulo-endothelial Stage of Malaria Parasites.**] *Klin. Woch.* 1943, June 12, v. 22, No. 24/25, 417–18.

Seventy-two cases of benign tertian malaria were observed in a German field-hospital near Lake Ladoga (Russia) during April and May 1941. The patients (soldiers) had not previously been abroad, except that many of them had been in France, but all were in the Lake Ladoga district in the autumn of 1941 and had remained there throughout the winter. They had received no medical prophylaxis in 1941 and had had no fever since the summer of that year. Hibernating mosquitoes could not be regarded as effective carriers of sporozoites and a new

invasion of infective mosquitoes could not have occurred because ice and snow were still on the ground when the illnesses began. The author therefore thinks that the soldiers must have been infected locally in the autumn of 1941 and that the plasmodia had remained throughout the winter without development, either in the erythrocytes or, more probably, in the cells of the reticulo-endothelial system. The long period of primary latency, or incubation period, might have been caused by the climate. The author regards these observations as clinical evidence in support of the view that an exoerythrocytic stage exists such as was shown to occur in birds by KIKUTH & MUDROW [this *Bulletin*, 1940, v. 37, 671; 1942, v. 39, 24, 399, and, of course, originally by JAMES and TATE, *ibid.*, 1937, v. 34, 589.] *J. F. Corson.*

SHONE, S. & PASSMORE, R. **Pneumonitis associated with Autohaemagglutination.** *Lancet.* 1943, Oct. 9, 445–6.

Autohaemagglutination, visible to the naked eye within two minutes of taking the blood sample, was observed in every one of a group of 54 Indian soldiers admitted to a hospital in the Middle East for varying degrees of inflammatory involvement of the respiratory tract. The symptoms ranged from those of laryngitis with slight fever to febrile pneumonitis with patchy consolidation of the lungs, as shown in nine cases by X-ray examination. In the severe cases there was high intermittent fever with abundant mucopurulent sputum and dyspnoea. In some there was leucocytosis, in one case the white corpuscles were 61,000. No special organism could be found in the cases in which sputum, blood, or lung-puncture material, was investigated. Apart from this group there was no special incidence of respiratory infections among the troops in the station. The cases were seen in the cool season when nights were cold and the days warm, sunny and dry. The observations were made at room temperature, which is stated to have been "at or about body temperature." The patient's serum agglutinated the red corpuscles of rabbits and sheep. On recovery agglutination ceased to occur.

All the patients had recently been stationed in a highly malarious camp near Delhi; 20 had enlarged spleens; and in nine, malaria parasites were found.

Control tests were negative in 60 healthy sepoys, in 42 aseptic surgical patients, and in 48 afebrile medical cases. They were positive in 20 of 37 chronic malaria cases; in 21 of 51 cases of tuberculosis; in two of 41 acute and chronic respiratory infections; in two of eight cases of infective hepatitis, and, in the only case of nodular leprosy which was tested. Among 35 severe battle casualties there were seven positive reactions, all in patients with chronic sepsis.

The association with malaria, and the possible analogy with the pneumonitis occurring in Rickettsial infections are discussed.

[The investigation supplies fresh evidence that malaria causes a condition of low resistance to respiratory infections. Damage to the reticulo-endothelial cells may be an important factor in the production of the haemagglutinins. Autohaemagglutination is hardly the right name for the reaction. The evidence suggests that the respiratory infection may be a complication or sequela of malaria.]

John W. D. Megaw.

TRUJILLO GUTIÉRREZ, C. El paludismo. Estudio clínico. [**Clinical Study of Malaria.**] *Rev. Facul. de Med.* Bogotá. 1943, Apr., v. 11, No. 10, 585–611.

This is an excellent clinical lecture on malaria, by a physician of much experience, in which the symptomatology and differential diagnosis are very fully treated. *Norman White.*

HOWIE, J. W. & MURRAY-LYON, R. M. **Tanret Reaction in Subtertian Malaria.** *Lancet.* 1943, Sept. 11, 317–20. [12 refs.]

Hitherto the practical application of the Tanret reaction has been largely confined to the control of prophylactic quinine administration. The valuable observations here recorded extend its sphere of usefulness. They concern 100 consecutive patients, admitted to hospital in Southern Nigeria suffering from subtertian malaria, and 53 healthy controls ; all were British soldiers. The usual treatment of the acute attack was 10 grains of quinine bisulphate in solution thrice daily for seven days ; thereafter 10 grains daily for three or four days, and then 5 grains a day. Precautions were taken to see that the drug was actually swallowed. Tanret's test was applied to every specimen of urine passed by these patients. The urine of 88 patients showed positive reactions consistently throughout the treatment of the acute attack ; all these patients made rapid recoveries. In seven men no quinine was detected in the urine ; they were seriously ill until they were given intravenous quinine. Thereafter positive Tanret reactions were obtained and recovery was rapid. Five patients gave positive reactions at irregular intervals during the acute attack ; they recovered slowly and showed negative reactions during convalescence. The 53 healthy soldiers were each given 5 grains of quinine in solution. Their urine was examined 15, 30 and 60 minutes after taking the drug and then hourly until a strongly positive Tanret reaction was obtained. A final test was made 24 hours after the dose of quinine. All 53 men showed strongly positive reactions within five hours of taking quinine ; all reactions were negative after 24 hours. The time of appearance, and the duration of, positive reactions varied : 5 tests were positive at 30 minutes, 15 at 60 minutes, and the remaining 33 between two and five hours. Five of the positives became negative within 10 hours ; others were not examined with this regard. Clinical notes are given of the twelve patients who showed negative or irregularly positive reactions during the treatment of the acute attack. In one patient, an extreme case, the Tanret reaction remained negative throughout the 24 hours following the intravenous injection of 10 grains of quinine. Doses of quinine by mouth were increased in this case to 60 grains a day, for one day only, and then only were Tanret reactions positive throughout 24 hours. This patient had suffered from repeated attacks of malaria. In other cases intravenous injections resulted in positive reactions and thereafter quinine given by mouth produced positive reactions, in doses which before the injection had consistently given negative reactions. The authors discuss the possible association between some abnormality of quinine metabolism and blackwater fever. They suggest that quinine dosage in treatment and prophylaxis should be controlled and adjusted for each individual by the Tanret test. If this were done less might be heard of quinine resistant strains of malaria. *Norman White.*

BRAUN, K., CZERTOK, J. & KORNBLUETH, W. **An Unusual Case of Quinine Idiosyncrasy.** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1943, Dec., v. 37, No. 3, 221–4.

An interesting case of primary hypersensitiveness to quinine is described. The ingestion of a very small dose (0·1 gm. of quinine hydrochloride) produced severe symptoms, prominent among which were rigor, hyperpyrexia, diarrhoea, abdominal pain, vomiting and headache. The rigor and associated symptoms closely simulated those of an attack of malaria, a disease from which the patient had never suffered. A patch-test with quinine ointment gave a positive reaction.

Norman White.

LOUGHLIN, E. H., BENNETT, R. H., SANTORA, E. & MATTUCCI, S. **Clinical Toxicity of Atabrine Dihydrochloride (Quinacrine Hydrochloride U.S.P. XII). A Controlled Comparative Study of the Toxicity of American and of Foreign Atabrine when administered in Doses commonly employed in the Prophylaxis of Malaria.** *War Medicine.* Chicago. 1943, Sept., v. 4, No. 3, 272–9.

This describes an investigation to study whether American mepacrine (atabrine) was more toxic than foreign mepacrine, as had been claimed on the basis of certain preliminary work. The subjects were 85 patients with tuberculosis and 64 prisoners in a penitentiary. The materials were American mepacrine, foreign mepacrine A (made from German materials by German processes ; used for the patients), foreign mepacrine B (made from German materials by American processes ; used for the prisoners), and a placebo made to look like mepacrine. The dosage was either 0·1 gm. four times a week or 0·2 gm. twice a week. At each institution the subjects were divided into four groups, which were arranged so that each group took the placebo for three weeks, the American mepacrine for three weeks and one of the foreign mepacrines for three weeks, the order being varied in the different groups.

Severe symptoms included severe nausea, vomiting, abdominal cramps and diarrhoea ; some of these occurred among the tuberculous patients while taking the placebo and they were probably due to the tuberculosis. Minor symptoms included pain in the chest and poor appetite. The incidence of indisposition due to gastro-intestinal symptoms after the placebo, and after American and foreign mepacrines, is shown in the accompanying table.

As a psychological check the prisoners were asked leading questions about symptoms which could hardly be caused by mepacrine, and in response 41 complained of ringing in the ears, 7 had pain in the arms, and 14 were restless. The incidence of all symptoms diminished as the experiment proceeded. Since the symptoms among the tuberculous patients (corrected for those probably due to tuberculosis) were not significantly more frequent than those among the healthy prisoners, it is concluded that troops living under conditions of physical hardship should not be more liable to toxic reactions from mepacrine than persons living under more normal conditions. The symptoms as a whole were transient and usually mild, and, accordingly, a total weekly dosage of 0·4 gm. mepacrine di-hydrochloride should cause no disability and only minor and infrequent indisposition.

[This work proves (1) that American mepacrine (atabrine) is no more toxic than the mepacrine manufactured from German materials, and

(2) that normally the prophylactic administration of mepacrine does not cause important toxic reactions. However it sheds no light on the problem of why mepacrine occasionally causes acute severe abdominal symptoms in a high proportion of the men taking it.]

Indisposition due to Nausea, Vomiting and Diarrhoea.

	85 Tuberculous patients		64 Prisoners		Combined percentage of symptom-days
	Man-days	Percentage of symptom-days	Man-days	Percentage of symptom-days	
Placebo ...	2,352	2·42	1,848	0·87	1·74
Foreign mepacrine— A	1,533	3·92			} 4·00
B			1,092	4·12	
American mepacrine	1,470	5·44	1,092	1·56	3·79
All mepacrine	3,003	4·67	2,184	2·84	3·89

[The results are given throughout in terms of symptoms and of symptom-days and it is impossible to determine how many of the subjects were affected by these toxic manifestations.]

F. Hawking.

Aziz, M. **A Simple Device for destroying Adult Mosquitoes, House-Flies and other Household Pests by the Use of a Flame Thrower.** [Correspondence.] *Trans. Roy. Soc. Trop. Med. & Hyg.* 1943, May, v. 36, No. 6, 364–5.

If the spray from an ordinary "flit-gun" be ignited by means of a burning wick 2–2½ inches in front of the spray nozzle, a tongue of flame 1½–2 feet long and 6–8 inches wide is produced at each stroke. This is useful for killing mosquitoes and other pests. The wick is led from the oil container through a tube soldered on to the container; petroleum insecticides or light fuel oil may be used.

Charles Wilcocks.

Tattersfield, F. & Potter, C. **Biological Methods of determining the Insecticidal Values of Pyrethrum Preparations (particularly Extracts in Heavy Oil).** *Ann. Applied Biol.* 1943, Nov., v. 30, No. 3, 259–79, 11 figs.

Parkin, E. A. & Green, A. A. **A Film Technique for the Biological Evaluation of Pyrethrum-in-Oil Insecticides for Use against Stored Product Insects in Warehouses.** *Ann. Applied Biol.* 1943, Nov., v. 30, No. 3, 279–92, 5 figs. [13 refs.]

MARTIN, J. T. **The Preparation of a Standard Pyrethrum Extract in Heavy Mineral Oil, with Observations on the Relative Toxicities of the Pyrethrins in Oil and Aqueous Media.** *Ann. Applied Biol.* 1943, Nov., v. 30, No. 3, 293–300, 1 fig. [21 refs.]

NICOLE, J. E. **Malaria in Neuro-Syphilis 1923–43.** *J. Mental Sci.* 1943, July–Oct., v. 89, Nos. 376–77, 381–9, 7 charts.

WALETZKY, E. & BROWN, H. W. **Studies on the Mode of Action of Quinine in Avian Malaria.** *J. National Malaria Soc.* Tallahassee, Fla. 1943, v. 2, No. 1, 53–62, 2 figs.

The treatment of *P. lophurae* infections in ducks with quinine has been used to investigate the possibility that a metabolic product of this substance is the active agent in malaria. The drug was administered intravenously in large doses when young trophozoites predominated in the blood, and the effects of different treatments were judged by their influence on the reproductive rates of the parasites as compared with those in controls. Estimations of quinine in the blood were also made.

The duration of the plasmodicidal effect of quinine was determined by giving birds a single dose of the drug, followed by inoculation with infected blood at various intervals of time. By comparison with the reproductive rate in control and treated birds, quinine was shown to exercise an effect for at least 12 hours. The level of quinine in the blood fell rapidly and the amount present was very small after a period of 8 hours. High quinine levels in the blood of the host corresponded with low rates of reproduction and *vice versa*. In spite of the high correlation between various factors, the possibility that a metabolic product of quinine was the active agent could not be excluded.

Exposure of parasites to the action of quinine for 4 hours in the fowl host prevented reproduction in fresh birds. In another experiment quinine was given to a normal bird, which was infected after a definite time. At various intervals after infection, other normal birds were inoculated with its blood. The results showed that exposure to quinine for 2 or 3 hours *in vivo* greatly depressed reproduction.

Infected blood was incubated at 36°C. *in vitro* in the presence and absence of quinine. On inoculation to fresh fowls the reproductive rates of the parasites were determined. It was found that a concentration of 50–100 times more quinine was required *in vitro* than *in vivo* to affect the reproductive rates.

No definite evidence was obtained from these experiments to exclude a metabolic product of quinine as the active agent in the malaria infection studied. *J. D. Fulton.*

HEWITT, R. I. & RICHARDSON, A. P. **The Direct Plasmodicidal Effect of Quinine, Atabrine and Plasmochin on** *Plasmodium lophurae.* *J. Infect. Dis.* 1943, July–Aug., v. 73, No. 1, 1–11, 3 charts & 36 coloured figs. on 1 pl. [21 refs.]

In this paper the general and specific changes are described which occur in the parasites after administration of effective drugs to ducks infected with *P. lophurae*. The results of such treatment have been

measured quantitatively by inoculating infected blood from drug-treated donors into fresh hosts and observing the course of the subsequent infection. Support is afforded for the view that the drugs employed had a direct action on the parasites. The quantitative methods employed are of value in assessing the effectiveness of new compounds.

Degenerative changes in *P. lophurae* as a result of drug treatment depend on a number of factors such as the nature of the drug, dosage, frequency and mode of administration. Pentamidine given orally produced no morphological changes in *P. lophurae,* whereas much smaller doses given intramuscularly had a marked effect. Emphasis has been laid on the nature of the changes produced in the parasite by doses of various drugs causing a definite effect, and on the extent to which these changes control the nature of the resulting infection in fresh hosts.

The morphological changes produced in *P. lophurae* by oral administration of quinine, plasmoquine and atebrin to the host, at the peak of infection, are described in detail and illustrated along with those caused by pentamidine. The changes are brought about most rapidly by plasmoquine and most slowly by atebrin. From the nature of the changes seen in stained films it was possible to name the drug used in treatment. Other drugs cause changes corresponding with their chemical constitution in relation to that of the three standard types of antimalarial.

Morphological changes in the parasites caused by incubation of infected blood with various drugs were also investigated. The *in vivo* and *in vitro* changes produced by plasmoquine were very similar but degenerative changes were not produced by quinine or atebrin *in vitro* under the conditions employed.

After treatment of donor-birds with quinine, atebrin or plasmoquine it was found that the degenerate forms produced persisted for some days in the blood of the recipient-birds. Infections produced by the blood of plasmoquine-treated donors deviated most from those in the controls. As already stated, the evidence obtained suggests that quinine, atebrin and plasmoquine attack *P. lophurae* directly, and also that plasmoquine acts unchanged. The mechanism of the action of these drugs is not yet clear, but there is no evidence that they stimulate phagocytosis or other immune reactions. *J. D. Fulton.*

PESSÔA, S. B. & BARRETO, M. P. Notas sobre a ação antimalárica de algumas substancias. VII. Falsas quinas, lupanina, clorofilato de sodio e azul da Prussia. [**Antimalarial Action of certain Substances.**] *Acta Med.* Rio de Janeiro. 1943, Apr.–May, v. 11, Nos. 4–5, 63–7. English summary.

In *P. cathemerium* infection of canaries, no antimalarial action was found with the following: total extract of *Strychnos brasiliensis* and *S. macracanta*; the alkaloid lupanine, from *Lupinus albus*; sodium chlorophyllate and Prussian blue. *Charles Wilcocks.*

MANWELL, R. E. & EDGETT, Ruth. **The Relative Importance of certain Factors in the Low Temperature Preservation of Malaria Parasites.** *Amer. J. Trop. Med.* 1943, Sept., v. 23, No. 5, 551–7, 5 figs. on 1 pl.

The experiments reported on the low temperature preservation of malaria parasites by Manwell [this *Bulletin*, 1943, v. 40, 756] have been

continued with the object of finding the best conditions and technique to be employed. The blood of ducks infected with *P. lophurae* was used. The value of various modifications in technique was assessed by the nature of the infection resulting in ducks when inoculated with the preserved samples as well as by examination of stained slides. It was found advantageous to employ tubes thinner than those used in the earlier experiments, and by this means a strain of human toxoplasma could be preserved which was not previously possible. Mechanical rotation of the blood-tubes while freezing was preferable to the manual method. The temperature at which freezing was carried out was less important than that of storage, and when frozen at a temperature as high as −10°C. parasites have remained viable. The best temperature for storage has not yet been determined. Gradual deterioration of parasites has not been noted when they are stored at temperatures between −75° and −50°C., and they have remained viable for at least 244 days. The degree of infection of the stored blood exerted little effect except that if infection was intense all the erythrocytes appeared to be more fragile. *J. D. Fulton.*

Reichenow, E. & Mudrow, Lilly. Der Entwicklungsgang von *Plasmodium praecox* im Vogelkörper. [**Development of** *Plasmodium praecox* **in Birds.**] *Deut. Tropenmed. Ztschr.* 1943, June 15, v. 47, No. 12, 289–99, 3 figs.

The authors have investigated the exoerythrocytic cycle of development of *Plasmodium praecox* following the injection of sporozoites into the tissues of canaries. The majority of the injected sporozoites are destroyed, only a small number which have entered cells of the reticulo-endothelial system being successful in proceeding to further development. A successful sporozoite within the cell becomes, as other observers have noted, a uninucleate rounded body which for four hours shows no increase in size. It then commences to grow, till at the end of 16 hours it has reached the stage of the first nuclear division. Four hours later the two daughter nuclei divide, and again four hours later the products of this division also divide. Further nuclear divisions occur, a period of about four hours intervening after each series of divisions. Generally there are six such divisions before segmentation into merozoites occurs, the whole development from the sporozoite to the mature schizont occupying 36 hours. Theoretically there should be 64 merozoites, but as some nuclei fail to divide the actual number is between 32 and 64. These merozoites enter cells of the reticulo-endothelial system and again produce schizonts and merozoites as before. The third cycle commences, but instead of all the schizonts developing in the same way, in some the nuclear division proceeds further, to produce 128 or more, instead of the 64 nuclei. The merozoites produced by the schizonts with the larger number of nuclei are smaller than the others. They possess little cytoplasm and smaller nuclei. These small merozoites are designated micromerozoites, in contradistinction to the larger macromerozoites, the schizonts producing them being termed microschizonts and macroschizonts, respectively. Occasionally, a microschizont will appear during the second cycle, but this is unusual. The micromerozoites are in size and structure like those which result from the schizonts developed within the red blood corpuscles, and they are destined to enter the red blood corpuscles to commence the erythrocytic phase of development.

The macromerozoites on the other hand do not invade the red blood corpuscles. They only enter cells of the reticulo-endothelial system. In the fourth endothelial cycle most of the schizonts are microschizonts, while in the fifth cycle practically all are of this type. After this no further endothelial development can be detected. At the end of the third endothelial cycle the first micromerozoites to be produced invade the red blood corpuscles, and commence the erythrocytic infection, which can first be detected 114 hours after the injection of sporozoites. Most of these erythrocytic forms develop into schizonts at very much the same rate as did the endothelial forms. Sixteen hours are needed for development to the first nuclear division, and four hours for each subsequent division. A schizont with 16 nuclei will have developed in 28 hours: others with up to 24 nuclei will have developed within 32 hours. It is noteworthy that the earliest produced micromerozoites, after entering the red blood corpuscles, do not all develop into schizonts. As many as 30 per cent. develop into gametocytes, so that it is clear that some of the micromerozoites are already sexually differentiated when they invade the red blood corpuscles. The first batch of micromerozoites which enter the red blood corpuscles reach maturity at the same time, so that there is a high degree of synchronism. With the advent of an increasing number of micromerozoites this synchronism is rapidly lost, so that the established blood infection is characterized, as is well recognized, by a complete lack of synchronism. The authors are careful to point out that the data they have given in this, their preliminary communication, apply only to the particular strain of *P. praecox* they have discussed. They promise to publish a complete and detailed account of their work at some future date. [For observations on *P. gallinaceum* see this *Bulletin*, 1943, v. 40, 116.]

C. M. Wenyon.

TRYPANOSOMIASIS.

MARTINS, A. V., VERSIANI, V., TUPINAMBA, A. A., SOBRINHO, A. T., TORRES, A., LASMAR, J. E. & TEIXEIRA, A. A. Sobre 25 casos agudos de molestia de Chagas observados em Minas Gerais. [**Twenty-five Cases of Chagas's Disease seen in Minas Geraes.**] *Mem. Inst. Biol. Ezequiel Dias.* Belo Horizonte. 1939 & 1940, v. 3 & 4, 5–51, 20 figs. on pls.

Between December 1939 and December 1941 the authors have observed 25 cases of Chagas's disease in the State of Minas Geraes, 20 of them in the Municipality of Bambuí, which has a well-equipped hospital and is central for patients to apply for treatment; three in the Municipality of Luz adjacent to Bambuí, and one each in Rio Paranaiba in the west of the State, and Grão Mogol in the north. The character, or at least the severity, of the disease varies in different parts of the State. Thus, towards the south-west and near the frontier with São Paulo it is more serious and acute and more often diagnosed; in other parts, as along the banks of the Rio das Velhas, in the centre of the State, not a single acute case was met with in the two years, although more than 20 per cent. of the people were found to be harbouring *T. cruzi*. [This is a high figure; an account of the survey is to be published later.]

Of the 25 cases recorded in detail in this article 18 presented the initial Romaña's sign, six had generalized oedema, more marked on the face. In 20 the trypanosome was seen when the blood was first examined; in another it was found a fortnight later on re-examination, two were negative to this but were proved by xenodiagnosis. One, a child of four years, died and leishmanial forms were seen in large numbers in sections of the myocardium; in one other the diagnosis seems to have been made on clinical appearances only. The article is well illustrated.

H. Harold Scott.

MAZZOTTI, L. & LEÓN, L. A. Infección experimental por *Trypanosoma cruzi* de *Triatoma carrioni* del Ecuador. [**Experimental Infection of** *T. carrioni* **with** *Trypanosoma cruzi.*] *Medicina.* Mexico. 1942, v. 22, No. 411, 191–3, 1 fig. [Summary taken from *Rev. Applied Entom.* Ser. B. 1943, Nov., v. 31, Pt. 11, 213.]

Of 19 examples of *Triatoma carrioni*, Larr., taken in southern Ecuador, in 1941, none was found naturally infected with *Trypanosoma cruzi*. Most of them refused to feed and died, but two nymphs were fed on a healthy animal for two months, and on 5th January 1942 one of them was fed on a mouse that had been infected with *T. cruzi* and showed a few trypanosomes in the blood. On 9th February, developmental forms of *T. cruzi* were found in the dejecta of this nymph. The inhabitants state that the adults of *Triatoma carrioni* fly into houses by night, attracted by light, but as nymphs have also been found in dwellings, the adults presumably continue breeding indoors even if they do come from outside.

WOOD, S. F. **A New Locality for** *Trypanosoma vespertilionis* (=*T. cruzi*?) **in Bats in the United States.** [Research Notes.] *J. Parasitology.* 1943, Oct., v. 29, No. 5, 363.

In July 1941 R. O. INGMAN found trypanosomes in blood smears from a bat of the species *Antrozous pallidus pacificus*, caught seven miles west of Plymouth, Amador county, California. The trypanosomes appeared to be identical with *T. vespertilionis*. DIAS (*Trans. Roy. Soc. Trop. Med. & Hyg.*, 1937, v. 31, 260) found what appeared to be the same trypanosome in the same species of bat at Pinole, Contra Costa County, California. This trypanosome closely resembles *T. cruzi* and the author thinks that it is important to search for *T. cruzi* in mammals and blood-sucking arthropods in the central valley of California, especially the area of the foothills of the Sierra Nevada mountains.

J. F. Corson.

LEISHMANIASIS.

PEÑA-YÁNEZ, A. Ueber die Entwicklung der *Leishmania donovani* im Organismus und ihre Beziehung zu der Temperaturkurve. [**The Development of** *Leishmania donovani* **in the Organism, and its relation to the Temperature Curve.**] *Deut. Tropenmed. Ztschr.* 1943, Apr. 15, v. 47, No. 8, 193–8, 2 figs.

The study of cases of kala azar in Spain has led the author to a realization of the similarity of this disease to malignant tertian malaria.

In both, he states, the parasites, apart from the gametocytes in the case of malaria, are rarely seen in the peripheral blood. On this account nearly all cases of kala azar are at first mistaken for malignant tertian malaria. In malaria the parasite reproduces in the internal organs, and there is a correlation between the stage of development of the parasite and the temperature curve. It occurred to him that a similar correlation might exist between the development of *Leishmania donovani* and the temperature curve in kala azar, which actually bears a close resemblance to that of the malarial infections. By examining cases of kala azar repeatedly by spleen or sternum puncture the author claims to have traced a definite cycle of development for the leishmania, of which there are four types or stages. The first is an elongated form with a rounded end in which the nucleus lies. The other end is pointed, while the kinetoplast is apparently absent: the second resembles the first but is broader, while a dot-like kinetoplast is visible: the third type is oval or spherical with a distinct rod-shaped kinetoplast: the fourth type is still larger, with signs of nuclear and protoplasmic division. Presumably the products of division are parasites of the first type. Now the author maintains that in cases in which a regular attack of fever occurs each day, repeated examination of the spleen or bone marrow by puncture will show in the stained films that the majority of the parasites are extracellular, and are in process of multiplication as the attack of fever comes on. Later, when the temperature commences to fall, multiplication is complete and the smears will show the daughter form of the first type. The cycle typically occupies 24 hours, but is only clearly seen in those cases which exhibit the well-marked rise in temperature. In other cases there is considerable irregularity in the cycle, which results sometimes in the temperature curve indicating a fever of the continuous type. When the temperature increases are not marked the smears will reveal a parasite degeneration indicative of the success of the protective processes of the host, but if the attacks of fever are severe, no such degeneration is evident.

The paper is illustrated by two temperature charts, in one of which are depicted the various types of parasite described in relation to the rise and fall of the temperature. The observations recorded are admittedly very difficult to make, and it must be questionable whether the author has been justified in drawing his conclusions from the somewhat meagre details available to him. *C. M. Wenyon.*

VERSIANI, O. Leishmaniose visceral americana. [**American Visceral Leishmaniasis.**] *Brasil-Medico.* 1943, June 19 & 26, v. 57, Nos. 25 & 26, 268–71, 3 figs. [10 refs.] English summary.

A man, 30 years of age, made a journey on foot from the north-east of Brazil across the plateau of Bahia to the state of Minas Gerais. He was ill on arrival, suffering from fever with enlargement of the liver and spleen. No response being obtained to antimalarial treatment, further investigations were instituted, with the result that leishmania were demonstrated by spleen puncture. Though this is the first case of kala azar to be identified in the state of Minas Gerais, no conclusion as to its autochthonous nature can be made, as the man concerned had recently passed through Bahia, where kala azar is of frequent occurrence. *C. M. Wenyon.*

FERRO-LUZZI, G. Studio sul kala-azar in Eritrea. [**Kala Azar in Eritrea.**] *Boll. d. Soc. Italiana di Med. e Igiene Trop.* (Sez. Eritrea.) Asmara. 1943, v. 2, No. 3, 5–13. English summary (4 lines).

Though cases of kala azar in human beings and dogs have been reported by various observers in Eritrea, the disease is of sufficient rarity to justify the author in giving an account of nine cases which have come to his notice during the four years 1939–1943. All the patients were adults, varying in age from 21 to 39 years; six were Europeans and three natives. The symptomatology of the disease was that of the Mediterranean kala azar. *C. M. Wenyon.*

KIKUTH, W. & SCHMIDT, H. Zur Therapie der Leishmaniosen im Mittelmeerraum. [**Therapy of the Leishmaniases in the Mediterranean.**] *Deut. Tropenmed. Ztschr.* 1943, May 15, v. 47, No. 10, 247–52.

The authors discuss the chemotherapy of kala azar, and note that response to neostibosan therapy is better in Indian and Chinese kala azar than in the Mediterranean or Sudanese forms of the disease. Investigations carried out with the object of discovering a remedy which would be better for those forms which were difficult to cure with neostibosan, and which would possibly be useful for mass therapy in India and China, led to the discovery of solustibosan, the first pentavalent antimonial (antimony gluconate) which could be prepared in solution ready for injection. The total dose of this solution for intravenous or intra-muscular injection (containing 20 mgm. of pentavalent antimony per cc.) was 2 cc. for each kgm. of body weight. It was found subsequently that the single dose usually employed could be exceeded, and that a dose of 10 or 12 cc. could be administered, so that a total of 120 to 180, or even 240 cc. could be given with safety. As the quantities to be injected with these higher doses were large, trials were made of more concentrated solutions, with the result that two new preparations were established :—

(1). Concentrated solustibosan five times the original strength, in which 1 cc. contains 100 mgm. of pentavalent antimony. Pharmacological tests showed that in spite of the solution being hypertonic, it was absorbed without irritation from the tissues. This solution was thus capable of being administered intramuscularly as well as intravenously.

(2). Solustibosan suspension, in which 1 cc. contains 54 mgm. of pentavalent antimony. The solustibosan in powder form is suspended in oil. It seemed probable that the drug would be slowly absorbed from the oil depot so that the body would be under the action of the antimony for a longer time. Tests on kala azar hamsters showed that while eight injections of the watery solution involving the administration of 500 mgm. of solustibosan per kgm. of body weight (in all, 1,080 mgm. of antimony) sufficed to bring about a cure, the same result was obtainable by a single intramuscular injection of 6 cc. (324 mgm. of antimony) of the suspension per kgm. of body weight.

Pharmacological tests on mice showed that a 20 gm. mouse would tolerate a subcutaneous injection of 0·5 cc. (1,350 mgm. of antimony per kgm. of body weight, as against 860 mgm. of antimony administered in watery solution). Röntgen ray examinations showed that the oil depot had been completely absorbed in 48 hours.

Clinical trials carried out in China with the suspension showed that a single injection did not effect a cure, though it was evident that this

result was obtained with more certainty and with a smaller number of injections than with the solustibosan solution. RAMOS, SALA and SAN JOSÉ treated children in Spain. The intramuscular injection of the suspension was well tolerated, both locally and generally. The dose was 1 cc. per kgm. of body weight, the full course consisting of five injections, given at two-day intervals. In over 90 per cent. of the cases treated early, there was a rapid response, the fever disappearing after the first injection. Only in severe cases and in those in which other remedies had failed was the response less satisfactory, so that a second course of injections was necessary. These observers also report on the use of concentrated solustibosan by intramuscular injection. The drug was well tolerated and gave good results. Satisfactory results were obtained by administering the drug every 12 hours, a total quantity of 0·4 cc. per kgm. of body weight being given in 10 injections in five days. The concentrated solution has not yet been tried in adults, for whom the dose would presumably be one-fifth that of the usual unconcentrated solution.

In another direction the concentrated solution has been found useful. VILANOVA [this *Bulletin*, 1943, v. 40, 828] has employed it for the treatment of oriental sore by local injection. For sores on the eyelids, nose and ears it is the method of choice. These observations of Vilanova have led the author to test the concentrated solution on experimental oriental sore infections in the tails of mice. By administering 12 local injections it has been possible to eradicate the leishmania, a result which could not be obtained in previous tests with other preparations. The author expresses a hope that the results so far reported mean that with the two new preparations a definite advance has been made in the therapeutics of Mediterranean kala azar and oriental sore. *C. M. Wenyon.*

LOZANO MORALES, A. El "solustibosan concentrado" en el tratamiento del kala-azar infantil. Ensayos previos. Pauta alterna. [**Concentrated Solustibosan in the Treatment of Infantile Kala Azar.**] *Med. Colonial.* Madrid. 1943, June 1, v. 1, No. 6, 372–82, 5 figs. [20 refs.]

The author gives an account of his experience in the treatment of five cases of infantile kala azar in Spain with concentrated solustibosan solution, which contains 100 mgm. of pentavalent antimony per cc. [see KIKUTH above]. The drug was administered intramuscularly in the gluteal region, the total dose in each case being 0·6 cc. for each kgm. of body weight. For weights up to 30 kgm., the author recommends the amounts of the first, second and subsequent doses, and the total quantity, shown in the following table :—

Patient's weight	1st dose	2nd dose	Later doses	Total
10 kgm. ...	0·2 cc.	0·4 cc.	0·6 cc.	6 cc.
15 ,, ...	0·3 cc.	0·6 cc.	0·9 cc.	9 cc.
20 ,, ...	0·6 cc.	0·6 cc.	1·2 cc.	12 cc.
25 ,, ...	0·7 cc.	0·8 cc.	1·5 cc.	15 cc.
30 ,, ...	0·9 cc.	0·9 cc.	1·8 cc.	18 cc.

The injections were made on alternate days, the first two doses representing a divided dose to avoid accidents from hypersensitivity ;

they are followed by nine doses. The response to treatment was good. There was a marked increase in weight, reduction in the splenomegaly and return to normal of the blood picture. In none of the cases was there any evidence of toxicity, either local or general, nor was there any tendency to development of antimony-resistance. The final conclusion is that of the various preparations of antimony used for the treatment of kala azar, this concentrated solution of solustibosan is the one to be preferred, because it is non-toxic, gives satisfactory results and, being in solution in ampoules, is ready for immediate use.

C. M. Wenyon.

HENRY, A. J. **Instability of Stilbamidine in Aqueous Solution.** [Correspondence.] *Nature.* 1943, Dec. 11, 690–92.

The author, working in Khartoum, has continued the investigation of the changes which stilbamidine in aqueous solution undergoes when exposed to the action of light. His results are in substantial agreement with those obtained in earlier experiments by FULTON and YORKE; BARBER, SLACK and WIEN; FULTON; and GOODWIN [this *Bulletin* 1943, v. 40, 23; 376; 683; 684]. New products of the reaction have, however, been obtained and the author suggests that, after prolonged exposure to diffuse daylight, one or both amidine groups in the parent molecule undergo hydrolysis to the corresponding amides. These two products of hydrolysis have been isolated and "characterized with fair certainty," and the presence of ammonium chloride in the solution was established. He believes that *cis*-stilbamidine and its hydrolytic products are also formed at the same time. On the other hand, when stilbamidine solutions were exposed directly to tropical sunlight, evidence was obtained that a polymerization product 1, 2, 3, 4-tetra (4′-amidino phenyl) cyclobutane was formed from two molecules of the parent substance and also *cis*-stilbamidine. The author suggests on theoretical grounds that 2-(4′-amidino phenyl)-6-amidino indene should be a stable product and might possess all the advantages of stilbamidine as a therapeutic agent.

[Somewhat different experimental conditions have been employed by the various workers to bring about the changes in stilbamidine. In the original experiments Fulton and Yorke exposed a 1 per cent. solution to sunlight, while Barber *et al.* irradiated a 10 per cent. solution with the light from a mercury-vapour lamp with apparently the same results. In the present experiments the conditions were as described above; the strength of the solution employed was not stated.]

J. D. Fulton.

FEVERS OF THE TYPHUS GROUP.

BAKER, A. C. **The Typical Epidemic Series.** *Amer. J. Trop. Med.* 1943, Sept., v. 23, No. 5, 559–66.

In this unconventional paper the author speculates on the origin and evolution of diseases belonging to the typhus, relapsing-fever, and yellow-fever groups. He suggests that the infecting agent of each of these diseases originated as an infection of a "primary arthropod," probably a tick or mite. Taking louse-borne typhus as an example and

assuming that the primary arthropod is the rat-flea—though he thinks that an acarine may really have been the first arthropod host of the Rickettsiae—the stages of evolution would be as follows :—

Type of Disease	*Transmission*
Class 1.—The arthropod disease	Flea to flea only.
Class 2.—The animal disease	Flea to rat, rat to flea, indefinitely.
Class 3.—The endemic human disease	As Class 2, but incidental transmission from flea to man, never man to flea.
Class 4.—The intermediate human disease	Flea to man, then man to louse which is the "secondary arthropod" and which then takes on the transmission characteristic of Class 5.
Class 5.—The epidemic human disease	Louse to man, man to louse, indefinitely.
Class 6.—The regressing human disease	Louse to man, then the cycle ends owing to low virulence of the infection. Brill's disease is given as an example; the "secondary arthropod has dropped out of the picture" and the disease has become a "mild disease of man only."

The mite-borne and tick-borne typhus fevers have not progressed beyond class 3. In tick-borne relapsing fever the primary arthropod alone is concerned ; in the louse-borne disease classes 4 and 5 come into evidence through the intervention of the secondary arthropod, the human louse.

In yellow fever it was formerly assumed that the only classes were 4 and 5, recently class 3 has been discovered in the form of jungle yellow fever ; the author believes that a class 2 type, transmitted by a hitherto undetected primary arthropod, will be discovered.

The author believes that the existing differences in the strains of the infecting agents of each of the above diseases are accounted for by differences in the species of the primary arthropods concerned.

John W. D. Megaw.

GRATCH, I. **Bacillus** *Proteus OX19* **agglutinated by the Serum of Pregnant Women.** *Amer. J. Surgery.* 1943, June, v. 60, No. 3, 411–14. [11 refs.]

During the preliminary stages of a survey of the incidence of Rickettsial diseases in the Philadelphia area it was noticed that the sera of pregnant women agglutinated *Proteus OX19.*

An investigation directed towards this point gave the following results :—

	Sera examined	Positive to *OX19*	Negative
Men	412	22	390
Non-Pregnant Women	295	7	288
Pregnant Women ...	505	505	0

A further finding was that all the non-pregnant females who had positive reactions were suffering from carcinoma. So also were two of the males with positive reactions; two other males had been vaccinated with *Proteus vulgaris*; in the remaining 18 no cause could be found for the positive reaction.

The stage of pregnancy at which the reaction becomes positive and the time taken for it to become negative after delivery remain to be discovered. In one case of a 12-year-old girl the reaction was weakly positive at an early stage while the diagnosis was difficult and the Friedman test was still negative; 12 days later there was agglutination at a titre of 1–1,024.

A rapid simple test was employed in which a drop of serum was mixed with a drop of *OX19* suspension on a glass slide. The results were controlled by carrying out a simultaneous standard reaction in 50 pregnant women, and the titre was found to range from 1–256 to 1–1,024.

The implications of the test are discussed; it may prove to be a simple early test for pregnancy, and even for malignant tumours, subject to certain limitations, some of which are already known while others remain to be worked out.

[These findings are of exceptional interest. Apart from the further investigations planned by the author, it will be important to find whether other organisms besides *Proteus OX19* are agglutinated in similar conditions.

The remarkable uniformity in the Weil-Felix titre in pregnancy suggests that the substance which agglutinates *OX19* is produced with greater regularity in the altered metabolism of pregnancy than in that due to the presence of Rickettsiae. The findings also raise the broad question of the possibility of using agglutination reactions as indicators of certain unusual by-products of metabolism.

Neither the findings nor the speculations to which they give rise detract from the practical value of the Weil-Felix test as an aid to the diagnosis of typhus fever, except in the case of pregnant women, and perhaps also in the case of malignant disease; they suggest, instead, the possible opening of a fresh chapter in the romantic history of the agglutination reaction associated with the names of WILSON, WEIL, and FELIX.] *John W. D. Megaw.*

MORNAS, P. L'hémodiagnostic du typhus en milieu rural. [**A Typhus "Haemodiagnostic" Outfit in Rural Areas.**] *Bull. Inst. Hyg. Maroc.* 1942, v. 2, 53–9, 1 chart.

A handy case containing the requisites for carrying out Brumpt's rapid agglutination test has been put on the market by the firm Laboratoires Dausse. This outfit has been found very useful in rural areas for the immediate diagnosis of typhus and typhoid fevers, both during life and after death. Its immediate issue to medical and public health workers is strongly recommended. Six cases are described to illustrate the help that can be expected from its use.

[No description is given of the outfit, but there would be no difficulty in designing a pocket case to contain phials of the Proteus and other suspensions, glass slides, pipettes, etc., needed for one of the rapid

bedside tests. Outfits of this kind may soon be regarded as indispensable for isolated medical men both in war and in peace.]

John W. D. Megaw.

KLIGLER, I. J. & OLEJNIK, E. **Specific Diagnosis of Typhus Fever by Rickettsial Agglutination.** [Correspondence.] *Nature.* 1943, Nov. 27, 627–8.

Comparative tests were carried out to determine the agglutination responses of patients to the Rickettsiae of murine and epidemic typhus. The results are shown in the table:—

	Endemic Rickettsia Titre	Epidemic Rickettsia Titre	Weil-Felix Titre
6 cases confirmed murine typhus in 2nd week	250 to 400	0 to 100	100 to 1,000
6 cases confirmed epidemic typhus, about 8th day	0 to 100	80 to 600	0 to 200

In 12 louse-infested typhus patients the reactions to epidemic typhus Rickettsiae were: four reacted 1–80; five, 1–160; and three, 1–320.

Up to the time of writing only one patient reacted in the same titre to both epidemic and murine Rickettsial strains; the titre in this case was 1–640.

Guineapigs tested four weeks after recovery from murine and epidemic infection gave the following reactions:—

	Titre							
	0	20	50	100	200	300	400	800
After murine infection 6 guineapigs reacted to								
(*a*) murine Rickettsiae					2	2	1	1
(*b*) epidemic Rickettsiae	1	2	1	2				
After epidemic infection 9 guineapigs reacted to								
(*a*) murine Rickettsiae			6	3				
(*b*) epidemic Rickettsiae					2		6	1

Formolized vaccines of two murine strains "T" and "K" from Tunis and Palestine, and from two epidemic strains "A" and "R" from Addis Ababa and Russia, were used to immunize rabbits whose agglutination reactions for each of these Rickettsial strains were tested two weeks after the last dose of vaccine had been injected. The results in typical examples were:—

Rabbit vaccinated with Strain	Endemic-Rickettsia Titre		Epidemic-Rickettsia Titre		Weil-Felix Titre
	Strain K	Strain T	Strain A	Strain R	*Proteus OX19*
Murine K ...	800	400	200	±200	50
Murine T ...	200	800	100	50	100
Epidemic A	±100	100	800	200	100
Epidemic R	±100	100	200	800	±200

Absorption tests confirmed these results, which show not only a decided difference between the epidemic and murine antigenic pattern, but also that different strains of a given type, whether murine or epidemic, contain different antigenic elements so that vaccines should be polyvalent if full protection is to be ensured. *John W. D. Megaw.*

REGAMEY, R. Le typhus exanthématique. [**Exanthematic Typhus.**] *Schweiz. med. Woch.* 1943, Oct. 30, v. 73, No. 44, 1321–7.

This is a good clinical account of louse-borne typhus; it is on orthodox lines and is up to date except that no reference is made to Rickettsia-agglutination reactions.

The author subscribes to Mooser's simple classification of the fevers of the typhus group, in which only three main forms are recognized, *viz.*, (1) typhus exanthematicus (vectors, louse and flea; and *OX19* agglutination), (2) Rocky Mountain and boutonneuse types (vectors, ticks; and *OX2* agglutinins), (3) tsutsugamushi type (vectors, mites; and *OXK* agglutinins). He rightly condemns the use of a multiplicity of meaningless names for identical forms of the fevers. He also agrees with MOOSER in regarding the murine infection of rats as the permanent reservoir of epidemic human typhus, whose Rickettsia is merely a variant strain of the murine Rickettsia. The differences between these two strains break down in practice so frequently that they cannot be regarded as consistent features.

A mouse-lung killed vaccine has been adopted as the standard preparation for the Swiss army, it consists of a mixture of *Rickettsia mooseri* and *R. prowazeki* in the proportion of three of the former to one of the latter. The Cox yolk-sac vaccine has been found difficult to prepare; suitable strains have not been easy to find and the yield from the inoculated yolk sacs has been highly irregular. Living vaccines are regarded as unreliable. *John W. D. Megaw.*

CALDERON, BARCA, RICO-AVELLO & RICO. Sobre una epidemia de rickettsiosis en Alcazarquivir. (Año 1942.) [**An Outbreak of Rickettsiasis in Alcazarquivir.**] *Med. Colonial.* Madrid. 1943, Sept. 1, v. 2, No. 3, 178–219, 7 graphs, 17 charts & 1 fig. [39 refs.]

In this outbreak 65 cases of louse-borne typhus occurred in a town of Spanish Morocco in the months of May, June, July and August, 1942. There were nine deaths. A petechial rash was seen in six cases, of

which five were fatal; in the other cases there was only an insignificant roseola or no rash at all. The duration of the fever was uniformly about fourteen days. The Weil-Felix reactions were: positive in 56 cases, usually at titres of 1–250 to 1–500; persistently negative in 6; and not tested in 3. The strain employed is designated as "*OX* and X19." In two cases *Proteus X2* and *XK* also reacted, but at the low titre of 1–50.

Dried Proteus cultures were used in trials of a rapid bedside test; the reactions corresponded with those of the standard test in strongly positive cases, but when the Weil-Felix titre was 1–100 to 1–200 the results were inconclusive.

The leucocyte count ranged from 11,000 to 17,000; there was complete absence of eosinophiles, pronounced lymphopenia, and a deviation to the left of the Arneth index.

The chief features of this and four other outbreaks in Spanish Morocco are given in tabular form; three of the other outbreaks showed similar clinical features except that in one of them the Weil-Felix reaction is said to have been negative in all the cases. In the fourth outbreak the fever lasted seven days, the Weil-Felix reaction was negative, there were no mental disturbances, leucopenia was a pronounced feature, and no death occurred in any of the 25 cases. [On the evidence supplied a diagnosis of dengue seems probable in this outbreak.]

John W. D. Megaw.

AVTSIN, A. P. **Conjunctival Exanthem in Spotted Typhus.** *Arch. Pathology.* 1943, Aug., v. 36, No. 2, 158–62, 1 fig. [From the Chair of Pathological Anatomy of the First Moscow Medical Institute, U.S.S.R.]

Red points or spots were seen in the conjunctiva of 94 per cent. of typhus cadavers examined at the Moscow Clinical Institute for Infectious Diseases. In many cases these were the only distinctive naked-eye sign that could be detected after death. They were absent only in cases in which death occurred late, and from some complication such as pneumonia.

The spots were rounded or oval in shape; these and the points were observed on the conjunctiva of the upper and lower eyelids, sometimes also of the sclera; they were of the nature of petechial haemorrhages.

By microscopical examination they were found to have resulted from vasculitis of the capillaries and small arteries, which were thrombosed or affected by nodule formation. Secondary degenerative changes were seen in the overlying conjunctival epithelium.

Similar spots were found in septic endocarditis and meningococcal septicaemia. They could be detected in only 27 per cent. of patients in the hospital wards and so are not likely to be of much help in diagnosis during life. Their significance lies in the fact that when found after death they justify a suspicion of typhus fever, even in the absence of clinical data.

John W. D. Megaw.

V. STOCKERT, F. G. Die psychischen Störungen bei Fleckfieber. [**Psychic Disturbances in Typhus Fever.**] *Deut. med. Woch.* 1943, July 9, v. 69, No. 27/28, 506–8.

A very long list is given of the mental disturbances observed in typhus fever. Only a few of these can be referred to.

In the early stages somnolence is the chief feature, in some cases there is a tendency to katatonia; soon there is restlessness or delirium; picking at the bed clothes is frequently observed; there may be a tendency to self-injury or even suicide. There may be euphoria or depression, or an alternation of these states. When delirium is pronounced the rash usually appears early. In restless patients the movements tend to be choreiform. A dream-state may occur in which the patient believes that he has received a high decoration from the hands of the Führer or that he has performed impossible feats. The Korsakoff syndrome is often simulated and by the second week the speech is nearly always affected, the articulation often being like that of a general paretic. Hallucinations of hearing are common. Active delirium is of bad omen.

The expansive hallucinations above referred to are more frequent towards the end of the fever or in convalescence. Weeks or even months after defervescence there may be serious mental disturbance such as changes in disposition or criminal tendencies. Defects in the eye muscles persist for three months in 10 per cent. of the cases. Mental deterioration may be permanent. It is of the same type as in encephalitis.

The period of convalescence should not be less than three months, it may be up to six months. *John W. D. Megaw.*

MRUGOWSKY, J. Impfschaden nach Fleckfieberschutzimpfung? [**Suspected Harmful Effect of Typhus Vaccine.**] *Deut. med. Woch.* 1943, June 11, v. 69, No. 23/24, 447–8.

A German nursing sister aged 30 died of fulminating typhus fever two days after receiving her third dose of a carbolized typhus vaccine prepared at the Robert Koch Institute, Berlin, by the Gildemeister and Haagen method. Other samples of the same batch were tested and found to be sterile and of normal toxicity to guineapigs and white mice. The dose was given at the unusually short interval of five days after the second dose. On the day of administration the temperature rose to 40°C. Next day the patient was admitted to hospital complaining of weakness, and body pains, especially in the arm into which the injection had been made. The face was flushed, the temperature was 38·2°C. and there was albuminuria. No other symptoms were noticed till the evening when there was stiffness of the neck.

Early on the following morning the temperature was 37°C., the pulse 72, and the injected arm could not be raised. On the same morning the patient suddenly collapsed and died while passing a stool.

At the autopsy a polymorphic rash was seen, chiefly on the legs; the naked-eye and microscopical findings were characteristic of typhus fever.

The author discusses the possible harmful effect of the short interval of five days between the doses and raises the question whether the fulminating character of the attack may have been due to the extra dose of typhus toxin given late in the incubation period. [In fact, the old problem of the "negative phase" is revived.] He mentions evidence that a dose of typhus vaccine given during the incubation period may hasten the onset in some cases and increase the severity of the attacks. *John W. D. Megaw.*

CAMACHO TÉLLEZ, J., DIAZ ANGULO, A., ROMERO PÉREZ, M. & SALAZAR, G. Relación de algunos casos de tifo murino observados en la Costa del Estado de Sinaloa. [**Note on a Few Cases of Murine Typhus seen in the Coastal Region of the State of Sinaloa, Mexico.**] *Medicina.* Mexico. 1943, Sept. 10, v. 23, No. 443, 353–5.

In the course of an investigation in which blood cultures were being made for the detection of typhoid infection a non-motile strain of *Proteus OX19* was isolated from a patient whose symptoms suggested typhus fever.

In two other cases which occurred shortly afterwards, in December 1942, the same organisms were isolated. The disease was diagnosed as murine typhus. Three further cases occurred in May 1943; in these the symptoms were similar and the Weil-Felix reaction was strongly positive. One of the patients came from a place where fleas were exceedingly abundant. The disease was regarded as murine because of the duration of 15 to 16 days and the rapid convalescence. No reference is made to any laboratory tests except the Weil-Felix reaction. *John W. D. Megaw.*

SHELLEY, H. M. **Tick Typhus.** *East African Med. J.* 1943, Sept., v. 20, No. 9, 300–301, 2 figs. on 1 pl.

Five cases of tick typhus were seen in three years in Europeans in Tanganyika. All the cases occurred in persons who had recently been living or travelling in the bush, and who had been exposed to special risk of bites by ticks.

The attacks resembled louse-borne typhus except that the onset was gradual, the rash was prominent and extended to the palms, soles, and face, and was followed by staining, which lasted several weeks. Also there was often a primary sore and associated lymphangitis at the site of the tick bite. The Weil-Felix reaction varied from negative to strongly positive; in one case the following titres were recorded:—*Proteus OX19*, 1–500; *OXK*, 1–25; *OX2*, 1–1,000.

One case is described in which these features were present, and the others are said to have been very similar. *John W. D. Megaw.*

READING, B. & KLINT, H. A. **Clinical Observations on Spotted Fever in the Gulf Coast Area of Texas.** *Texas Rep. Biol. & Med.* 1943, v. 1, No. 2, 97–104, 4 figs.

Four fatal cases of "spotted fever" [tick-borne typhus] occurred in a locality in Brazoria, Texas. These have already been reported by the authors [see this *Bulletin*, 1944, v. 41, 30] but more details are now given, and from these points of interest have been collated (see table below).

In the first case there was no history of tick bite; in the second a tick identified as *Dermacentor variabilis* was found on the back of the neck at the onset and there was swelling of the lymph nodes of the neck. In the other two cases intracellular Rickettsiae were found by ANIGSTEIN and BADER [below; also this *Bulletin*, 1943, v. 40, 386] in the endothelial cells, and guineapigs inoculated with the blood were later found to be immune to strains of Rocky Mountain spotted fever.

Case	Date	Age	Day of disease on which death occurred	Leucocyte counts	Reaction to *Pr. OX19*	Rash
1	June 1937	5	12th	10,000 to 20,000	1–320 (11th day)	Over whole body, petechial
2	July and Aug. 1939	7	30th	7,000 to 18,000	1–320 (17th day)	Macular, then petechial with ecchymotic patches, widespread
3	June 1942	3	10th	3,900 to 15,500	Neg. (6th day)	Petechial, all over body, haemorrhagic patches
4	June 1942	10 months	9th	2,800 to 4,600	Neg. (? day)	Macular, then petechial, all over body, diffusely haemorrhagic

John W. D. Megaw.

ANIGSTEIN, L. & BADER, M. N. **Investigations on Rickettsial Diseases in Texas. Part 1. Epidemiological Role of Ticks Common to the Gulf Coast in relation to Local Spotted Fever.** *Texas Rep. Biol. & Med.* 1943, v. 1, No. 2, 105–16, 2 figs.

Sera of various animals in the Gulf Coast region of Texas were tested against *Proteus OX19*, *OX2* and *OXK*. The reactions in most of the positive cases were about the same to all three strains and were as follows :—

	Negative	Positive	Usual titres
Dogs, heavily infested with *Rhipicephalus sanguineus* ...	2	19	1–80 to 1–160
Dogs, not heavily infested with ticks	67	10	1–80 to 1–160
Cows, infested with *Amblyomma americanum* and *A. maculatum*	60	18	1–80 to 1–160
Cows, tick-free...	6	1	1–80
Hogs	102	22	1–160 to 1–320

Ticks collected from the same area were investigated but the results are not stated in such a way as to make them easy to summarize.

About 2,500 adult *R. sanguineus* from apparently healthy dogs, and about 2,000 larvae and nymphs hatching from deposited eggs of the same species of tick, were divided into lots ; suspensions were prepared and inoculated intraperitoneally or subcutaneously into guineapigs in the usual way. Details of the experiment are not given, but it is stated that the majority of the guineapigs reacted with fever after an incubation ranging from 2 to 11 days. In one case the infection was carried through nine passages involving 94 guineapigs. A scrotal reaction was seen in only two of a large but unstated number of guineapigs ; smears of the tunica were negative.

Of two rabbits inoculated intraperitoneally with tick (*R. sanguineus*) suspensions one developed pneumonitis, and lung sections contained numerous Rickettsia-like bodies. The reaction to *OX19* of this animal's serum was positive, 1–160, on the 12th day, having been negative previously.

In a later experiment 98 *R. sanguineus* adults were inoculated into four guineapigs, one of which became febrile on the 4th day and developed a scrotal reaction. The testicles, examined on the 6th day, showed microscopical changes like those found in experimental "spotted fever." Attempts to passage the infection failed.

A. americanum collected from cattle in Cleveland, Texas, where cases of the spotted fever type had occurred two years previously, were tested in the same way in 1941 ; a highly virulent infection was caused in the guineapigs, but no mention is made of the isolation of Rickettsiae.

A less virulent infection was caused by *A. maculatum* collected in the same area, but the strain could not be established by passage through guineapigs. *John W. D. Megaw.*

ANIGSTEIN, L. & BADER, M. N. **Investigations on Rickettsial Diseases in Texas. Part 2. Experimental and Epidemiological Studies on an Outbreak of Spotted Fever in the Gulf Coast.** *Texas Rep. Biol. & Med.* 1943, v. 1, No. 2, 117–40, 1 graph & 6 figs. [16 refs.]

This paper contains a detailed report of the isolation and investigation of two strains of Rickettsiae from the blood of patients 3 and 4 of the series of cases described by READING and KLINT (above).

The patients were infected at the same time and place, presumably from the same source, and the infection was equally virulent in both, causing death between the 9th and 10th days; yet one strain was more lethal to guineapigs, causing a fatality rate of 12 per cent. against 5 per cent. for the other. The virulence for animals, therefore, did not give a true index of that for human beings.

Scrotal reactions in guineapigs were infrequent; when they did occur in later passages they were slight, but in the later passages Rickettsiae were recovered from tunica smears.

The experimental disease in guineapigs corresponded with that caused by some strains of Rickettsiae of Rocky Mountain spotted fever transmitted by *Dermacentor andersoni*.

The results of immunity tests were—(1) By tests in guineapigs the two local strains gave almost complete reciprocal cross immunity. (2) Guineapigs convalescent from the disease caused by each strain were immune to Rocky Mountain spotted fever. (3) In one set of tests it was found that guineapigs which had recovered from Rocky Mountain fever had little or no immunity to the local strains, but in another series immunity was complete. (4) An interesting finding was that no cross immunity was found between either strain and two strains of louse-borne Rickettsiae. This finding is opposed to that of CASTAÑEDA and SILVA [this *Bulletin*, 1942, v. 39, 151] in which a pronounced degree of partial immunity was observed between *Rickettsia prowazeki* and *R. rickettsi*.

Egg-yolk vaccine of the Cox type prepared with *R. rickettsi* protected guineapigs against both of the local strains.

Suspensions of *Amblyomma americanum* from dogs in the locality where the cases occurred caused a febrile reaction in one of two guineapigs inoculated with suspensions made from seven ticks. The infection was passaged to two other guineapigs which had febrile reactions lasting three to four days after an incubation of seven days. After recovery these animals reacted to the local strains with low fever after a long incubation period and were regarded as being partially immune.

The authors suspect that mild cases of "spotted fever" may occur in the locality and are wrongly diagnosed as "typhus." [The name "spotted fever" obviously refers to a tick-borne fever of the typhus group, and the name "typhus" to the flea-borne fever of the same group. Both of these names are rather ambiguous.]

John W. D. Megaw.

SIZEMORE, P. **Rocky Mountain Spotted Fever.** *Oklahoma State Med. Ass. J.* 1943, July, v. 36, 282. [Summary taken from *J. Amer. Med. Ass.* 1943, Oct. 9, v. 123, No. 6, 384.]

Sizemore reports observations in 7 cases of Rocky Mountain spotted fever. The cases occurred in a family in the town of Armstrong in

Bryan County, which is located in the south central section of Oklahoma. The family lived here for several years but had moved into a new, unpainted, green lumber house only a short distance from their previous home. The household consisted of a couple, their three children and the wife's mother. The latter, aged 67, died of the illness contracted by all of them. All developed what was first suspected to be typhus but later was identified as Rocky Mountain spotted fever. The attending physician, Dr. Flythe, aged 44, died of the disease. A man aged 47 who had stayed at the home of the family while the first three members were ill became ill and died. The rash suggested that this fatality was also caused by the Rocky Mountain spotted fever. Questioning brought out the fact that all members of the household had been bitten repeatedly since moving to the new house by ticks which infested the yard. The gopher proved to be the ticks' host in the Armstrong area. The use of vaccine in infested areas each year is indicated. This is best given in late winter or early spring. The vaccination should be completed at least ten days before the first expected exposure. The vaccine is not recommended for therapeutic use.

BAKER, G. E. **Rocky Mountain Spotted Fever. Nine Year Study of Wyoming Cases.** *Journal-Lancet.* Minneapolis. 1943, July, v. 63, 207. [Summary taken from *J. Amer. Med. Ass.* 1943, Oct. 9, v. 123, No. 6, 382.]

Baker points out the close resemblance of endemic typhus to Rocky Mountain spotted (tick) fever. The degree of protection afforded by vaccine and the duration of such protection vary. As a rule those vaccinated in the spring of the year retain a considerable degree of immunity for at least the remainder of that year. Treatment of tick fever is purely symptomatic and supportive in character. Bed rest with good nursing care is necessary. The author had occasion to study the various aspects of tick fever in a section of Wyoming where the disease occurs with considerable frequency. In 1934 Kamp and the writer received encouraging reports of responses obtained in typhus by use of neoarsphenamine dissolved in aqueous solution of metaphen. In the spring and summer of 1934 they used this treatment in 9 moderately severe cases of the disease. None of the patients succumbed to their illness. Since that time an average of 3 to 4 cases of tick fever have been under the writer's care each season. During the past eight years recovery has occurred in all cases so treated. A combination of the bactericidal action of metaphen, together with the spirocheticidal action of neoarsphenamine, on a micro-organism which is bacterium-like in character yet has staining properties similar to those displayed by spirochetes may be the secret of the success. In this treatment 0·3 Gm. of neoarsphenamine was dissolved in 10 cc. of an aqueous solution of 1 : 1,000 metaphen. The mixture was warmed and injected slowly into a vein. Administration is repeated at three or four day intervals. Three or four injections have customarily been sufficient to ameliorate the clinical picture so as to insure ultimate recovery. Should severe renal injury exist as a result of the infection, careful consideration must then be given the question as to whether the use of these medicaments is justified.

CAMERON, E. **Rocky Mountain Spotted Fever : Summary of Recent Literature dealing with Virulence and Therapeutic Value of Immune Rabbit Serum.** *Delaware State Med. J.* Wilmington. 1943, Aug., v. 15, 139. [Summary taken from *J. Amer. Med. Ass.* 1943, Nov. 6, v. 123, No. 10, 659.]

It has been accepted that the western strain of the virus of Rocky Mountain spotted fever is more virulent than the eastern strain and hence accompanied by a higher mortality rate. Observations have been made, according to Cameron, which indicate that this view is not entirely correct. Comparative studies on large numbers of cases from western and eastern states revealed that there was no significant difference in the fatality rate in comparative age groups. There is a significant difference between the fatality rates in the age group 40 and over and those of younger age groups. Immune rabbit serum given early following infection in an adequate dose gave the best results in repeated experiments on monkeys and guineapigs. In studying the human cases it was impossible to use an untreated group as a control. The fatality rates were compared in a series of 19 cases treated with immune rabbit serum after the third day of the rash and in a series of 52 cases treated on or before the third day of the rash. While the series are small, the inference is that immune serum is of value if used early in the infection. Up to the present there have been 13 cases reported in Delaware in 1943. There were three fatalities, in one of which immune rabbit serum had been given.

PIZA, J. de T. A vacina de Spencer-Parker, contra a febre maculosa, na prática sanitária. [**The Spencer-Parker Spotted Fever [Tick-Borne] Vaccine in Public Health Practice.**] Reprinted from *Arquivos de Cirurg. Clin. e Exper.* 1942, Oct.–Dec., v. 6, Nos. 5–6, 1329–57, 6 graphs. English summary.

The tick-borne "exanthematic typhus fever of São Paulo" or "spotted fever" has become a serious public health problem in some parts of Brazil. The number of cases and the range of distribution have been increasing rapidly in the past few years. The case-fatality rate is about 90 per cent. Since 1939 more than 10,000 persons in heavily infected localities have been vaccinated with the Spencer-Parker type of vaccine [a formol-phenol preparation of infected ticks, see this *Bulletin*, 1925, v. 22, 521 ; 1936, v. 33, 47] and the results have been highly satisfactory. In one place where the death rate in non-vaccinated patients had been over 82·0 per cent. it was reduced to about 8·1 per cent. in the vaccinated.

The special advantage of the vaccine in public health practice was that it kept the disease under control during the period in which areas were being systematically disinfested of ticks. In some of these areas the tick infestation was intense and the tick-infection rate was so high that rabbits and guineapigs kept in natural conditions became infected.

The vaccines used were prepared at the Butantán Institute of São Paulo and at the Rocky Mountain Laboratory at Hamilton. Both of these vaccines gave approximately the same degree of protection, and were followed by the same percentage of reactions.

In heavily infected areas it is recommended that revaccination should be carried out twice during the first year, and should afterwards be repeated yearly. *John W. D. Megaw.*

LIVESAY, H. R. & POLLARD, M. **Laboratory Report on a Clinical Syndrome referred to as "Bullis Fever."** *Amer. J. Trop. Med.* 1943, Sept., v. 23, No. 5, 475–9, 1 fig. & 1 chart.

This paper contains a report of an extensive series of laboratory investigations directed to finding the cause of the problematic short fever called Bullis fever [see this *Bulletin*, 1944, v. 41, 34].

Guineapigs inoculated by the intracerebral route with spinal fluid from patients developed a transient mild fever on the 9th day in several cases. In one case a serial passage was successful, but there was no apparent increase in virulence. Brain substance from reacting guineapigs inoculated by the intravenous route into developing chick embryos caused death within six to nine days, and the same result was obtained in five serial transfers by the same route.

In guineapigs inoculated with the blood of patients by the intraperitoneal route a low-grade febrile reaction lasting two days occurred consistently on the 9th to the 10th day. There was no scrotal reaction, but in two cases an aseptic fibrinous peritonitis was observed. Five serial passages were made in guineapigs and there was a progressive rise in the percentage of reactors. Smears from the spleens and peritoneal scrapings of the guineapigs showed small red-stained rods and coccoid bodies in the cytoplasm and nuclei when stained by Machiavello stain.

Biopsy specimens of the enlarged lymph nodes of patients were used to prepare films which, when stained by the Machiavello technique, showed small intracellular fuchsin-stained granules and rods; these were not seen in films stained by Wright's stain. Emulsions of the same lymph nodes caused a febrile reaction in guineapigs through three passages, the incubation period was 8 to 12 days, the temperature 104° to 104·5°F. and the fever lasted two to four days. There was no orchitis.

Rocky Mountain spotted fever was excluded by cross-immunity tests. By various serological and other tests typhus fever, Q fever, Chagas's disease, equine encephalomyelitis and lymphocytic choriomeningitis were also excluded.

About 150 ticks, mostly *Amblyomma americanum*, were collected at random in the affected area and tested by guineapig inoculation. One positive result was obtained in which intracerebral inoculation caused a rise of temperature to 106·2°F. for 24 hours on the 9th day.

It was concluded that "Bullis fever" is a previously undescribed syndrome, apparently caused by Rickettsiae which may be transmitted by "an arthropod vector, the tick or Trombicula, in the Camp Bullis area." *John W. D. Megaw.*

BARTONELLOSIS.

HOWE, C. **Immune Serum Therapy for Oroya Fever.** *Arch. Intern. Med.* 1943, Oct., v. 72, No. 4, 429–38, 5 figs.

The author records three cases of Oroya fever treated by intravenous injections of rabbit serum obtained in the following way: Four strains of *Bartonella bacilliformis* were obtained, three from Oroya fever patients and one from a Peruvian sandfly. These were maintained on Geiman blood-agar. For the purpose of immunizing rabbits a 5-day-old

culture at 28°C. was suspended in saline after centrifuging. An emulsion of a strength of two slants per cc. was made. One cc. was given to rabbits on each of three successive days, and, after a rest of 3–4 days, this course was repeated twice. One rabbit was given a suspension of formaldehyde-treated organisms, eight others had fresh suspensions. After this each animal was bled twice, perhaps three times. Their serum agglutinating titre was usually 1 : 2,560.

Three patients were treated with this, a man of 51, another of 21, and a lad of 15 years. The first had 10 cc. daily intravenously on the 20th to 24th days of disease, 50 cc. in all; the man of 21 had, on the 21st and 26th days of illness, 100 cc. and 150 cc. transfusions of whole blood (the donors had never had Carrión's disease) and from the 23rd to 27th days 10 cc. doses daily of the immune serum. The lad of 15 had a total of 60 cc., namely 10 cc. on the 8th, 10th, 12th, 13th, 14th and 17th days of illness.

In none of the three was there any very definite change in the clinical picture of the disease, but in the boy the typical miliary eruption appeared unusually early, on the fourteenth day of illness. Also, in all three there followed, shortly after the injections began, a distinct fall in the percentage of infected corpuscles, indicating that the serum has some effect in clearing organisms from the blood-stream. It is suggested that a stronger serum might be still more effectual. It remains to be determined whether the change in the number of infected corpuscles was merely coincident with or was directly consequent on the injections. Another effect noticed was a change in the character of the colonies on culture; instead of being finely granular and numerous, they were fewer, larger and coarser. The difference is well depicted in a photograph of the culture tubes. *H. Harold Scott.*

YELLOW FEVER.

SMITH, H. H., BEVIER, G. & BUGHER, J. C. **The Distribution of Yellow Fever in Colombia in Recent Years.** *Amer. J. Trop. Med.* 1943, Sept., v. 23, No. 5, 505–22, 1 fig. & 2 maps. [21 refs.]

After the last-known cases of yellow fever disappeared from the Colombian coastal towns about 1920, it was thought that the disease had been entirely eradicated from the country. Therefore the outbreaks which occurred in the interior towns of Bucaramanga in 1923, and in Socorro in 1929, were very difficult to explain and, had the diagnosis not been confirmed subsequently by laboratory tests, yellow fever might not have been accepted generally as the cause of the epidemics. With the establishment of the specificity of liver lesions as a means of diagnosing fatal cases of yellow fever and the discovery of the mouse protection tests for the demonstration of specific immune bodies in the blood, it became possible to carry out surveys to determine accurately the distribution of the infection throughout the country. Since 1931, therefore, a considerable amount of epidemiological information has been accumulated which demonstrates clearly that the jungle type of yellow fever is probably present continuously in certain areas of Colombia. The endemic zone comprises the Departments of Antioquia, Boyacá, Caldas, Cundinamarca, Santander, and Tolima, and the Intendencia del Meta. The results of immunity surveys make it appear probable that the disease has existed in recent years in other

widely separated parts of the country such as the Atrato Valley and the Colombian Amazon drainage. With the exception of a very small epidemic in Buenavista, Caldas, in 1937, no incidence of yellow fever transmitted by *Aëdes aegypti* has been observed in Colombia since 1929. *Hugh H. Smith.*

GILMORE, R. M. **Mammalogy in an Epidemiological Study of Jungle Yellow Fever in Brazil.** Reprinted from *J. Mammalogy.* 1943, May, v. 24, No. 2, 144–62, 4 figs. & 2 pls.

The author of this report is a zoologist who, from 1935 to 1938, was attached to the Yellow Fever Service maintained jointly by the Government of Brazil and the Rockefeller Foundation. During the period of his stay in Brazil, intensive studies on the possible rôle of wild animals in the epidemiology of jungle yellow fever were in progress. The types of traps which were found most useful for the capture of various animals are fully discussed and illustrated. From his considerable experience the author states his views on the keeping of proper field records, the collection and preservation of specimens for subsequent study, the collection and preservation of ectoparasites, the presentation of taxonomic information, and the methods of handling animals in the field. Useful data on the estimation of the age and growth rates of certain animals are given. This information is, of course, important when immunity surveys on animal populations are undertaken. Also some observations on the territorial movements of Cebus monkeys are reported. These animals have been suspected repeatedly of being of importance in the spread of yellow fever infection in forested areas.

[This paper will be of value to those who are concerned with the investigation of epidemiological problems in which wild animals may play a rôle.] *Hugh H. Smith.*

LENNETTE, E. H. & PERLOWAGORA, Alina. **The Complement Fixation Test in the Diagnosis of Yellow Fever. Use of Infectious Mouse Brain as Antigen.** *Amer. J. Trop. Med.* 1943, Sept., v. 23, No. 5, 481–504. [21 refs.]

The occurrence of specific complement-fixing antibodies in the blood of man and monkeys recently recovered from yellow fever has been known since 1929 [see this *Bulletin*, 1929, v. 26, 1004 ; 1931, v. 28, 719 ; 1932, v. 29, 576 ; 1933, v. 30, 3]. The antigens used in the early work were infectious monkey serum or liver extracts. Liver antigens were variable in antigenic activity and also occasionally gave rise to non-specific fixation of complement. Monkey serum was open to the objection that it was not only a less sensitive antigen than monkey liver, but also that its large content of antisheep amboceptor may produce falsely negative tests. The development of a virus neutralization test in mice proved to be a more accurate immunological method ; so the complement fixation test was discarded. Recent work by CASALS and PALACIOS [*Bulletin of Hygiene*, 1942, v. 17, 444] has resulted in obtaining highly satisfactory specific complement-fixing antigens from mouse brains infected with any one of a number of neurotropic viruses, thus avoiding the well-known highly anti-complementary properties of crude extracts of nervous system tissues. The authors felt it might be worth while to apply this new technique to immunological studies on yellow fever.

The antigen is prepared from freshly removed infected mouse brains which are triturated either in a mortar or in a ball mill. A 10 per cent. suspension of this brain paste is made with physiological saline containing 2 per cent. of an inactivated normal guineapig serum. This suspension is centrifuged after 24 hours' refrigeration. The supernatant fluid is drawn off and frozen and thawed five times in a mixture of alcohol and carbon dioxide ice. The antigen preparation is again centrifuged and the resultant relatively clear supernatant is removed and stored in the refrigerator in glass-stoppered pyrex bottles, merthiolate having been added to a final concentration of 1 : 10,000. The technique of the test is essentially the same as that recently described by LENNETTE and HORSFALL [see *Bulletin of Hygiene*, 1941, v. 16, 99] for influenza virus.

The authors conducted a series of experiments to demonstrate that the complement fixation test with yellow fever mouse brain antigens is biologically specific. Mouse sera containing antibodies to the viruses of lymphocytic choriomeningitis, St. Louis encephalitis, Japanese B encephalitis, Eastern equine encephalomyelitis, and West Nile disease gave negative tests in the presence of this antigen. As regards yellow fever, the specificity of the antigen was demonstrated by its ability to fix complement in the presence of serum from monkeys recovered from infection, but not in the presence of serum taken from the same animals prior to infection. In monkeys complement-fixing antibodies were found to be present in the blood serum at the end of the second week after infection. They reached a maximum titre during the third week or so and then gradually disappeared, leaving only small residual titre at the end of four months. Among persons vaccinated with the 17D strain of virus, only about 20 per cent. of those in whom no post-vaccination reaction occurred gave a positive fixation test. Among those who experienced relatively severe post-vaccination reactions, from 50 to 80 per cent. of the sera were capable of fixing complement. Sera from persons passing through natural yellow fever infection gave a high incidence of positive results. The results of the mouse protection tests and the complement fixation tests agreed in about 90 per cent. of the cases.

Although the complement fixation test is of no value for routine checking of post-vaccination results, it promises to be of considerable use in field immunity surveys. The rapid disappearance of complement fixing antibodies from the blood after infection indicates that when this antibody is present, the infection must have been relatively recent. The complement fixation test, therefore, may have a definite rôle in attempts to delineate recently endemic or epidemic areas of yellow fever.

Wassermann-positive sera tend to give non-specific reactions, which in the majority of cases can be eliminated by inactivation of the sera at 65°C. *Hugh H. Smith.*

BOL. OFICINA SANITARIA PANAMERICANA. 1943, Aug., v. 22, No. 8, 728–35, 3 figs. English summary. Recente vitória contra a febre amarela no Brasil. [**The Recent Conquest of Yellow Fever in Brazil.**]

"Having paid tribute to Brazil before for having eradicated the deadly *A. gambiae* in 1940, the Bulletin of the Pan American Sanitary Bureau once again congratulates that country for having also eradicated the *A. aegypti*, the yellow fever vector, in a feat hitherto considered practically impossible, from the States of Maranhão, Espírito

Santo, Minas Gerais, Goiás, Paraná, Santa Catarina and the Federal District. With the cooperation and under the leadership of the Rockefeller Foundation, the National Yellow Fever Service of Brazil has rendered and is continuing a service of great importance to the entire hemisphere. The campaign, in its planning, execution and consequences, evidences the true spirit of Panamericanism. A proof of the efficiency and success of this work has been the absence, since 1934, of outbreaks of yellow fever in the cities of Brazil, even though sporadic cases of jungle fever have occurred in the vicinity of the city limits of Rio de Janeiro. Viscerotomy has been one of the Service's notable achievements. Throughout the country 1,278 viscerotomy posts were established, and during the period from 1930 to 1941, 246,157 liver specimens were studied. Through this work the Service has been able to establish the exact geographical distribution of a large group of known diseases in Brazil as well as having discovered the existence of new ones. In the protection test work, the Service has examined the blood of 62,559 persons. During the period of November 1937 to December 1941, 2,107,916 persons have been vaccinated against yellow fever by the physicians of the Service. The main part of the laboratory work is done in Rio de Janeiro in the yellow fever research laboratories under the direction of the Rockefeller Foundation. Other small ones have been established for future field use in the following districts: Espírito Santo, Vale de Canaã (1932); Minas Gerais, Teófilo Otoni (1935); Pará, Marajó (1935); Goiás, Anápolis (1936); Paraná, Maracajú (1937); Espírito Santo, Vitória (1940). The National Department of Health of Brazil has, since January 1940, assumed complete charge of the yellow fever campaign."

LEWIS, D. J. **The Destruction of Mosquito Larvae by Terrapins.** *Sudan Notes.* 1942, v. 25, Pt. 1, 141. [Summary taken from *Rev. Applied Entom.* Ser. B. 1943, Nov., v. 31, Pt. 11, 214.]

In the course of a mosquito survey during the epidemic of yellow fever in 1940 in the Nuba Mountains, the author examined numbers of domestic water jars. In two villages near Talodi he found that 25 per cent. of the jars each contained one or two small water-tortoises (*Pelomedusa galeata*) and no mosquito larvae. If the tortoises were given mosquito larvae they fed voraciously on them, and larvae of *Aëdes aegypti*, L., were found in several of the jars that did not contain a tortoise. These two villages were among the few in which *A. aegypti* was common in the dry season (November), the reason being that water is stored for long periods in unusually large jars, and they are near the area where the epidemic is thought to have started.

THOMAS, H. D. **Preliminary Studies on the Physiology of *Aedes aegypti* (Diptera: Culicidae). I. The Hatching of the Eggs under Sterile Conditions.** *J. Parasitology.* 1943, Oct., v. 29, No. 5, 324–8. [10 refs.]

FRÓES, H. P. O estado de guerra e o problema mundial da febre amarela com especial referência ao Brasil. [**War and Yellow Fever with special reference to Brazil.**] *Brasil-Medico.* 1943, July 3–10, 17–24–31, & Aug. 7–14, v. 57, Nos. 27–28, 29–30–31 & 32–33, 284–9; 314–17; 335–6. [Refs. in footnotes.]

DENGUE.

McCarthy, D. D. & Brent, R. H. **An Account of an Outbreak of Dengue Fever in Dzaoudzi, Comoro Islands, January 1943.** *East African Med. J.* 1943, Sept., v. 20, No. 9, 293–8, 2 figs.

Dzaoudzi is an island 600 yards in diameter in the Comoro group, east of tropical East Africa. The rainy season is from December to March, and the average temperature is 90°F. Aëdes mosquitoes increase rapidly from the beginning of the rainy season.

The outbreaks of dengue began on the 1st of January, 1943; most of the attacks occurred between the 10th and the 21st of the month and the last attack occurred ten days later.

There were 59 cases; 30 in Africans, and 29 in Europeans. The onset was sudden, there was a rigor in half of the cases; the pulse was about 100 at the onset but soon fell to the normal rate. There was a rubeoloid rash against an erythematous background on the 2nd to the 4th day in 30 per cent. of the European patients and in 7 per cent. of the Africans. There was cervical or epitrochlear adenitis in six Africans and one European. Except for severe headache there is no reference to pains. Many of the permanent inhabitants have mild attacks yearly, but these last only two to three days, so that there is evidence of a partial degree of immunity resulting from previous attacks.

It was suggested by some medical men that the cases ought to have been diagnosed as sandfly fever, but no sandflies were found.

[The temperature charts reproduced in the article are typical of well-recognized forms of dengue, the fever seems to have lasted six days in most of the cases.] *John W. D. Megaw.*

PLAGUE.

Francis, E. **Twenty-Year Survival of Virulent** *Bacillus pestis* **Cultures without Transfer.** *Pub. Health Rep.* Wash. 1943, Sept. 10, v. 58, No. 37, 1379–82.

The title of this article gives exactly the conclusion arrived at, with the further detail that this happened with cultures on sloped beef infusion agar which had been kept at 10°C. Out of the 48 stored cultures tested 33 gave growth on subculture while 15 failed to do so. Most interesting are the facts regarding virulence, which was tested on guineapigs by subcutaneous inoculation :—(1) Eleven of the guineapigs survived the inoculation with little to show. (2) " Thirteen died near the end of the first week without showing significant gross change in spleen nor caseation of inguinal lymph nodes." (3) Three died with lesions of acute plague. (4) Six were killed before death and plague bacilli were isolated from heart blood, while acute plague lesions were evident at the site of inoculation, in the spleen and in the inguinal glands. The strain tested, P4-7, had been originally isolated from a California ground squirrel (*Citellus beecheyi*). *W. F. Harvey.*

AMOEBIASIS AND INTESTINAL PROTOZOAL INFECTIONS.

HORSTER. Die Bedeutung der Amöbenruhr für Nordafrika und ihre Bekämpfung. [**Amoebic Dysentery in North Africa and its Prevention.**] *Deut. Tropenmed. Ztschr.* 1943, June 15, v. 47, No. 12, 299–302.

The author discusses amoebic dysentery as it occurred amongst the German troops in North Africa. He adopts Westphal's view that *Entamoeba histolytica* is in the first place a harmless inhabitant of the intestine, and that actual amoebic dysentery only supervenes when the wall of the intestine has been injured so that invasion of the intestinal wall by the amoeba can take place. The commonest cause of such injury is bacillary dysentery, against which the newly arrived, unaccustomed troops have no immunity. Whereas bacillary dysentery and other bacterial disorders of the intestine are common amongst the newly-arrived troops, they rarely occur amongst the indigenous population, or troops which have been stationed for a considerable time in the country. In consequence amoebic dysentery is the common type of dysentery amongst the local inhabitants and seasoned troops, while bacillary dysentery is commonest amongst the new arrivals. The author notes that in 1941, of the admissions to hospital for intestinal disorders, 25 per cent. were found to have an *E. histolytica* infection, though in only some of these was the amoeba the cause of the trouble. It follows, therefore, that the easiest method of preventing amoebic dysentery is to take every precaution against the bacterial infections by the strictest cleanliness in the preparation of food, the maintenance of health by proper diet and the adoption of all the recognized sanitary measures. Furthermore, the author advocates the general employment of a Yatren-rivanol medication as a prophylactic or as a means of eradicating the lumen infection before invasion of the intestinal wall has occurred. In cases of amoebic dysentery treatment with emetine has to be undertaken. For satisfactory results every sanitary unit should have a good laboratory and a staff previously trained in diagnostic procedure. *C. M. Wenyon.*

ANGELINI, G. Beiträge zu dem Problem der Histolyticaträger in Venetien und zur klinischen Diagnose der Darmamoebiasis. [*E. histolytica* **Carriers in Venice, and Clinical Diagnosis in Intestinal Amoebiasis.**] *Deut. Tropenmed. Ztschr.* 1943, May 1, v. 47, No. 9, 228–30

In 1938 the author had occasion to examine for intestinal protozoal infections Italians returning from East Africa. In a group of 100 the following percentage infections were noted: *E. histolytica* 20; *E. hartmanni* 9; *E. coli* 27; *I. bütschlii* 8; *E. nana* 32; *D. fragilis* 8. Being unable to establish a relationship between the parasitological findings and the clinical symptoms, the author was led to study the infections in a group of 400 men who had never been in a tropical country. The infection percentages were: 4·75, 3·50, 21·0, 3·0, 21·25 and 1·25 respectively. A careful study of those infected showed that none of them was in ill health or revealed any symptoms which could be ascribed to the presence of *E. histolytica*. The author comes to the conclusion that in the district of Venice, where the study was made, this amoeba is normally a harmless inhabitant of the intestine, and that there is no justification for diagnosing a disease syndrome on the

mere presence of the amoebae (minute forms) or cysts in the stool. He admits that under certain conditions *E. histolytica* can invade the tissues and become the large tissue-invading amoebae which give rise to amoebic dysentery and liver abscess. Such cases, however, are of rare occurrence in the district investigated. In fact, if a search for *E. histolytica* were made in cases showing symptoms such as those of colitis which might be ascribed to amoebic infection, this parasite would rarely be found. In the case of the men repatriated from East Africa there were so many factors associated with residence in that country, apart from the amoebic infection, which might cause intestinal symptoms, that it was often difficult to arrive at a conclusion as to whether the condition was due to the amoebic infection or not.

C. M. Wenyon.

FAY, H. B. & JOHNSTON, C. A. W. **Amoebic Dysentery in the Northern Territory.** *Med. J. Australia.* 1943, July 24, v. 2, No. 4, 67–9.

In this paper seven cases of amoebic dysentery are discussed in some detail. The patients were admitted to a military hospital during the three months October 1942 to January 1943, and the interest lies in the fact that in only three was there any history of residence outside Australia. It was evident that in five cases, if not in all seven, the infection had been contracted in Australia. Three patients came from one unit, and it seems probable that the infection had been acquired in the camp.

C. M. Wenyon.

SNYDER, T. L. & MELENEY, H. E. **Anaerobiosis and Cholesterol as Growth Requirements of** *Endamoeba histolytica.* *J. Parasitology.* 1943, Aug., v. 29, No. 4, 278–84. [16 refs.]

A study of the cultural requirements of *Entamoeba histolytica* was made by using a liquid medium consisting of infusion of coagulated whole egg in 0·8 per cent. sodium chloride solution. Though growth in this medium was more luxuriant if starch was added, cultures could be maintained indefinitely without starch if subcultures were made every day. The cultures were made anaerobically, but, in order to ensure abundant bacteria, the medium was inoculated with bacteria and incubated aerobically for 24 hours before the entamoebae were introduced. In no case was it possible to maintain cultures without living bacteria. The investigation has led to certain conclusions regarding a number of growth factors, and the source from which they are derived in the culture medium.

	Factor	Source
1	Water	—
2	Inorganic salts	Ringer's solution, peptone.
3	Amino acids (?)	Peptone.
4	Carbohydrate (?)	Rice starch
5	Cholesterol	Cholesterol
6	Elimination of oxygen	Alkaline pyrogallate
7	Other reducing activity (?)	Cystein
8	Heat-labile factor	Serum
9	Other essential factors (?)	Anaerobic bacterium
10	Supplementary factors (?)	Liver extract, casein, etc. (?)

It is admitted that as it has not been found possible to replace living bacteria by the remaining unknown factors they supply, the results may be capable of other interpretations than those given to them.

C. M. Wenyon.

SHI LU CHANG. **Studies on *Entamoeba histolytica*. II. Observations concerning Encystation, Maturation, and Excystation of *E. histolytica*, and on the Longevity of Culture-induced Cysts in various Fluids and at Different Temperatures.** *J. Infect. Dis.* 1943, May–June, v. 72, No. 3, 232–41, 1 chart. [14 refs.]

In an earlier paper [this *Bulletin*, 1943, v. 40, 310] the author showed that for encystation of *Entamoeba histolytica* to occur it was necessary that the amoeba undergo an accelerated rate of multiplication, and that the *p*H of the medium be maintained at the correct level. In the maintenance of the *p*H level the accompanying bacterial flora is of importance. Thus a certain strain which was encysting readily after four months' culture not only ceased to give a good growth but also failed to produce any cysts. It was found that the *p*H had fallen to as low as 6·1. When the bacterial flora from another culture was introduced a favourable *p*H range was maintained, growth became abundant and good cyst yields were secured.

On the subject of chromatoids in the cysts the author has found that most of the newly formed cysts possess these bodies, but they tend to disappear from the cysts if they are kept in the warm incubator. It was also determined that immature cysts will not continue their development at room temperature or at that of the refrigerator, nor will they complete their development on return to the warm incubator after exposure to lower temperatures. Tests carried out on the viability of cysts showed that the suspending medium had little influence on the result. The important factor is temperature and, as other observers have noted, survival time is longer at lower than at higher temperatures. A formula is presented by which the probable survival time in days can be calculated from the temperature of exposure. An attempt was made to determine the minimal number of cysts which would give rise to a culture of amoebae. A suspension of cysts was diluted till one drop would contain a single cyst. Five groups of five tubes of culture medium were inoculated with 3, 5, 7, 9 and 11 drops of the diluted suspension. In the first group two produced cultures, in the second group four, while in the other groups all five tubes were positive. In cultures it was not possible to discover amoebae with more than two nuclei, while cysts with more than four nuclei were exceedingly rare.

C. M. Wenyon.

KIRKALDY-WILLIS, W. H. **Note on Two Cases of Obstructive Jaundice with Stenosis of the Bile-Ducts.** *East African Med. J.* 1942, Nov., v. 19, No. 8, 258–9.

Two cases of severe jaundice with fever which were recently admitted to a C.M.S. Hospital in Kenya are described. One patient was a man of about 40–50 years of age while the other was a woman aged about 40. The woman had an enlarged liver with pain and tenderness under the right costal margin; she received a course of emetine injections without benefit and exploration with a needle failed to show the presence of an abscess. The man showed no enlargement of the liver

and the pain was epigastric. In neither case were amoebae found in the faeces. Laparotomy was performed in each case and great stenosis of the hepatic, cystic and common bile ducts was found. In the woman the gall bladder appeared to be normal but contained white bile, while in the man it was hidden by loose adhesions and was red and thickened and the bile was viscid and bloodstained.

Both patients died, the woman three weeks after the operation, the man on the day following the operation, and autopsies were made. In both cases the hepatic, cystic and common bile ducts were "grossly stenosed," it being impossible to pass a probe down to the duodenal ampulla. The liver of the woman contained several large cavities with ragged walls but very little pus; in the man the liver appeared to be normal but section showed some cell destruction and the presence of amoebae. The pancreas and duodenum were normal in both and there were no signs of new or old inflammatory reaction round the ducts nor of glandular enlargement.

The author concludes that the stenosis was probably due to amoebic infection of the ducts in both cases and that the infection of the liver occurred later than that of the ducts. *J. F. Corson.*

KIRSH, D. & DIAZ-RIVERA, R. S. **Perinephric Abscess—a Previously Unreported Complication of Amebiasis.** *Amer. J. Med. Sci.* 1943, Sept., v. 206, No. 3, 372–8, 5 figs.

A man, 47 years of age, giving a history of a condition presumed to be amoebic dysentery, was operated upon for perinephric abscess, which completely resolved by drainage. Examinations of fresh preparations of the pus failed to reveal *Entamoeba histolytica*, which, however, was discovered on two occasions in blocked paraffin sections of the pus. Though the microphotographs of the amoebae reproduced in the paper are not entirely convincing, the authors state that the diagnosis "cannot be questioned." The paper gives a useful summary of literature dealing with amoebic infections in relation to the kidney.

C. M. Wenyon.

HERRLICH, A. Ein Fall von linksseitigem Leberabszess mit Durchbruch ins Perikard. [**Left-sided Liver Abscess with Rupture into the Pericardium.**] *Wien. klin. Woch.* 1943, July 16, v. 56, No. 27/28, 431–4, 1 fig. [18 refs.]

ROTHMAN, M. M. & LASKEY, Marion. **Survey of Protozoan Infection of the Staff of a Large General Hospital.** *Amer. J. Med. Sci.* 1943, Sept., v. 206, No. 3, 369–71.

The staff examined comprised nurses, porters, members of the business office and others who were not patients. In all, 306 persons were examined, and 44·4 per cent. of these were infected. Of the protozoa determined, the following percentage rates of infection were obtained: *E. coli*, 17·3, *E. nana*, 12·7, *G. intestinalis*, 10·1, *E. histolytica*, 3·6, *D. fragilis*, 2·3, *I. bütschlii*, 0·7, *C. mesnili*, 0·7, *E. hominis*, 0·3. *C. M. Wenyon.*

LÖRINCZ, F. & JURÁNY, Erika. Beiträge zur klinischen Bedeutung der Giardiasis. [**Observations on the Clinical Significance of Giardiasis.**] *Deut. Tropenmed. Ztschr.* 1942, Oct. 15, v. 46, No. 20, 505–9.

In a children's home in Hungary the authors undertook the study of 183 children from the point of view of giardia infections. The ages of the children varied from a few months to 12 years, and they were kept under observation for a year, examinations for infection being carried out each month. In some cases giardia was detected only once, in others the infection lasted for some months, while in others again it was detected at every examination. The children were carefully classified in groups, according as to whether the body weight or height were above or below normal. They were also grouped according to the presence or absence of symptoms of one kind or another. Those who were responsible for the classification of the children in these various groups were not aware of the parasitological findings, so it was carried out without bias. When finally the clinical and parasitological findings were examined together and subjected to a careful analysis it became clear that no outstanding case for the pathogenicity of giardia could be established. In the overwhelming majority of cases of infection this was quite symptomless, and even when certain troubles could be ascribed to it these were not of a serious nature. The development of the children was in no way impeded by the presence of giardia.

C. M. Wenyon.

YOUNG, M. D. & BURROWS, R. **Carbarsone Treatment for** *Balantidium coli* **Infections.** *Pub. Health Rep.* Wash. 1943, Aug. 20, v. 58, No. 34, 1272–3.

This report on the treatment of seven cases of infection with *Balantidium coli* indicates that carbarsone is an effective drug. The patients were treated at the South Carolina State Hospital during 1939; they constitute the largest group as yet treated in the United States. Two doses, each of 0·25 gm., were given daily for 10 days to four patients; cure was effected in one course in 2 and in two courses in 2. The infection disappeared, in the fifth case, after smaller doses. In the remaining 2 patients two doses, each of 0·5 gm., daily for 10 days eradicated the infection.

Examinations made for periods varying from 1 month to 4 years after treatment failed to reveal the parasites. [The patients were mentally defective white women; see this *Bulletin*, 1940, v. 37, 373.]

Charles Wilcocks.

RELAPSING FEVER AND OTHER SPIROCHAETOSES.

DIXON, K. C. **Some Serological and Biochemical Observations on Relapsing Fever.** *J. Roy. Army Med. Corps.* 1943, Oct., v. 81, No. 4, 193–7.

The author collected blood containing *Spirochaeta recurrentis* from 24 cases of relapsing fever among troops in Cyprus during the first half of 1942 and made Kahn tests on the resulting sera. Four gave

positive Kahn reactions, one a partially positive reaction and the remaining 19 gave negative reactions. It was only possible to follow up two of the seropositive cases; one was positive three weeks later and the other after four weeks.

In addition the urine from these patients was examined for urobilin by Slesinger's test and also by Ehrlich's test for urobilinogen. The great majority of the cases showed the presence of much urobilin in the urine, which is correlated with the fact that jaundice occasionally occurs in relapsing fever, and liver damage, insufficient to produce this symptom, may yet be extensive enough to cause urobilinuria.

E. Hindle.

BEESON, P. B. **The Problem of the Etiology of Rat Bite Fever. Report of Two Cases due to** *Spirillum minus.* *J. Amer. Med. Ass.* 1943, Oct. 9, v. 123, No. 6, 332–4, 2 charts.

The description of two cases of rat bite fever in the hospital at Atlanta, Georgia, at the end of 1942. One case was a white boy aged two years and the other a white woman aged 59, and both had been bitten by rats while sleeping. *Spirillum minus* was isolated from the blood of each patient by inoculation into mice, but the organisms did not appear in the blood of these animals until the 16th and 17th days. In view of the clinical similarity of infection due to *Streptobacillus moniliformis*, [see this *Bulletin*, 1942, v. 39, 693] blood cultures were made from both patients but with negative results. *E. Hindle.*

BURK, S. B. & HODAS, J. H. **Rat-Bite Fever. Case Report.** *Amer. J. Surgery.* 1943, June, v. 60, No. 3, 453–4. [10 refs.]

The record of a case of rat-bite fever in a white woman, aged 65, admitted to a New York Hospital nine days after being bitten by a rat. The wound had been cauterized the day after the bite and healed without any apparent complications until the day before admission. The patient developed typical symptoms of the disease, which responded markedly to treatment with neoarsphenamine administered intravenously. Blood culture was negative but a smear from the ulcerated wound showed the presence of spirilla. *E. Hindle.*

LEPROSY.

DE SOUZA-ARAUJO, H. C. O exame da linfa cutanea podera' servir para os diagnostico e prognostico da lepra, e mesmo para a sua classificação clinica. (Método Lleras.) [**Examination of Cutaneous Lymph in Leprosy.**] *Acta Med.* Rio de Janeiro. 1943, Apr.–May, v. 11, Nos. 4–5, 58–62, 7 figs. on 2 pls. English summary.

Examination of the lymph withdrawn by puncture of a gland has been used commonly in the diagnosis of leprosy. The method here described is of more recent date. Professor F. LLERAS ACOSTA initiated it in Colombia in 1937 and it goes, therefore, by the name of the "Lleras Method."

A clamp, 24 cm. in length, has the terminal 7·5 cm. curved and toothed, with 63 grooves, for compressing without bruising the tissues. After the skin is cleaned compression of a fold of it, 5 cm. in diameter, at

the edge of the suspected lesion is made up to the first notch in the handle and in five minutes the requisite degree of ischaemia is obtained. Then at three points in the fold puncture with a thick needle is made and in a minute there exudes a small drop of lymph at each puncture; this is collected and spread on a slide for bacterial examination. In patients undergoing treatment and who are progressing well the number of organisms in the lymph diminished and so may afford evidence of success in treatment and be of prognostic as well as of diagnostic value. *H. Harold Scott.*

MARIANO, J. Estudo anatomo-clinico de alguns casos de cancer e lepra. [**Cancer in Lepers.**] *Acta Med.* Rio de Janeiro. 1943, Aug.–Sept., v. 11, Nos. 8–9, 121–6, 4 figs. on 2 pls. English summary (3 lines).

There is a fairly widespread notion that there is some antagonism between leprosy and malignant disease, that cancer is rare amongst lepers. The author brings evidence to refute this error, citing five cases among patients in two colonies, Santa Isabel and Santa Fé, Minas Geraes. (1) A woman of 51 years with extensive mixed leprosy and with carcinoma of the right lower eyelid extending to the face. (2) A man of 51 years, clinically L1N3, with an ulcerous lesion of the left nostril. The diagnosis of this was "Leishmaniasis ? cancer," and was shown histologically to be the latter. (3) A man of 47 years, clinically L3N1 with a carcinomatous lesion very similar to the last. (4) A man, also 47 years of age, L1N3, with an extensive fibrosarcoma of the right leg. Amputation at the upper third of the thigh was performed, but death occurred less than three months later. (5) A man of 38 years, dying of adeno-carcinoma of the stomach. [The author does not mention the number of patients in the two leper colonies so we cannot gauge the proportion. Of the five recorded one occurred in 1935, two in 1937, one in 1938 and one in 1941.] *H. Harold Scott.*

HELMINTHIASIS.

NOGUEIRA RIVERO, P. Parasitismo a vermes en Marianao. [**Helminthiasis in Marianao.**] *Rev. Med. Trop. y Parasit.* 1943, Mar.–Apr., v. 9, No. 2, 18–22.

Between August 1937 and December 1942 the author examined 30,019 faecal samples, mostly from school children, for evidence of helminthic infestation. Of these 18,968 (63·1 per cent.) were positive. The commonest infestation was with *Trichuris trichiura*; it was the only one present in 12,034, but was present with others in another 5,658, or in 17,692 altogether, that is in 93·2 per cent. of the positives and 58·9 per cent. of the total examined. Next, but a long way behind, came Ascaris which was found alone in 543, alone and in combination in 4,408, or 14·6 per cent.; Ankylostome was seen in 2,686 (alone in 482) or 8·9 per cent., and Enterobius in 217 (0·7 per cent.), alone in 89. Examination was made by floatation in concentrated salt solution. Various forms of treatment were used: hexylresorcinol, chenopodium, tetrachlorethylene and others, but apparently in a small number of

cases only, 1,524 boys and 1,734 girls. The author concludes that the first-named, hexylresorcinol, is wonderfully efficacious in ascariasis, good in ankylostomiasis, poor for Trichuris infestation.

H. Harold Scott.

NATIONAL RESEARCH COUNCIL. DIVISON OF MEDICAL SCIENCES. **A Summary of Current Literature on Anthiomaline.** 36 pp., 1 chart. [63 refs.] 1943. Aug. 18. Prepared by the Office of Medical Information.

This is a useful compilation. In the first section is given an account of the pharmacology of the trivalent antimonial anthiomaline, the lithium salt of stibiothiomalic acid. The formula is :—

$$\left[\begin{array}{l} \text{Li O. CO. CH}-\text{S} \\ \qquad\qquad\quad | \\ \text{Li O. CO. CH}_2 \end{array}\right]^3 \text{Sb. } 9\text{H}_2\text{O}$$

Anthiomaline is supplied in 6 per cent. solution, 1·0 cc. of which contains about 0·01 gm. antimony. Dosage varies with the disease concerned, but in lymphogranuloma inguinale (that is, the disease in which the Frei skin test is positive, and known in the United States as lymphogranuloma venereum) it has been proposed to begin with 60 mgm. intramuscularly and to increase the dose of the single injections to a possible maximum of 300 mgm. until a total dose of 2–4 gm. has been reached. The injections are given three times each week and the course may be repeated after an interval of several weeks.

The doses should be regulated according to age and weight [those quoted above are presumably for an average adult]. Toxic reactions may take the form of rheumatoid pains arising several hours after the injection, or there may be salivation, retching, vomiting and abdominal pain. Slight fever may be provoked, and slight anaemia is a suspected, though not proved, sequel. No fatalities attributable to the drug have been recorded.

In the second section the therapeutic action of anthiomaline is considered. It is valuable in lymphogranuloma inguinale and appears to be useful in ulcerating granuloma of the pudenda (*i.e.* the disease due to infection with a leishmania-like organism and in which the so-called Donovan bodies are demonstrable in scrapings ; known in the United States as granuloma inguinale).

Some amelioration of the clinical condition has been recorded in filariasis, but the results are not, so far, very striking. In schistosomiasis, on the other hand, the results are uniformly good, and the drug is apparently useful in the treatment of oriental sore (either by local injections or wet dressings) and may be useful in kala azar. In a few cases of African trypanosomiasis anthiomaline in combination with moranyl gave good results.

Anthiomaline effected a probable cure in a case of infection with *Fasciola hepatica* and is reported as useful, in combination with sulphanilamide, in the treatment of trachoma.

Sixty-three papers have been consulted in the preparation of this summary.

Charles Wilcocks.

GOODWIN, L. G. & PAGE, J. E. **A Note on the Fate of Stibophen in the Body.** *Biochem. J.* 1943, Oct., v. 37, No. 4, 482–3, 1 fig.

Stibophen (Fouadin) is sodium antimony *bis*-pyrocatechol -3 : 5-disulphonate. It was thought that a determination of the relative

rates of excretion in the urine of the antimony and the sodium catechol disulphonate portions of the stibophen molecule would throw some light upon the fate of the drug in the body. The rate of excretion of antimony had previously been determined by the authors by means of a simple polarographic technique [this *Bulletin*, 1944, v. 41], and the same method was used in the present experiment. For the estimation of the catechol portion of the molecule a modification of Khalil's test for pyrocatechin in urine was used [this *Bulletin*, 1936, v. 33, 957]. The urine of volunteers who had received intramuscular or intravenous injections of stibophen (6·3 per cent. solution) or sodium catechol disulphonate solution (4·66 per cent.) was collected hourly for the first 6 hours and subsequently in 6–12, 12–24, and 24–48 hour fractions and tested as follows : 5 cc. of a tenfold dilution of ammonia solution (sp. gr. 0·880) was added to 5 cc. of urine, heated in a water-bath to coagulate any precipitate, and centrifuged ; 2 cc. of the supernatant fluid was mixed with 2 cc. of a freshly prepared solution containing 0·1 per cent. $FeSO_4$ and 0·5 per cent. sodium and potassium tartrate (Rochelle salt), then diluted with water to 10 cc., and the colour intensity was estimated with a Hilger " Spekker " absorptiometer by comparing it with standard solutions of stibophen in urine.

Catechol excretion was shown to be almost complete in about 6 hours, whereas the antimony excretion was much slower and followed a different course. The function of the catechol appears to be to keep the circulating antimony in solution in a non-toxic form while it is being absorbed by the liver or excreted by the kidney ; meanwhile the excretion of the catechol takes place independently of that of the antimony and at the same rate as that of an equivalent dose of sodium catechol disulphonate. *J. F. Corson.*

NEWMAN, H. R. **Transurethral Surgery in relation to Bilharziosis of the Bladder.** *J. Urology.* 1943, Oct., v. 50, No. 4, 440–45, 3 figs.

CANÇADO, J. R. Schistosomose mansoni. Estudo clínico e terapêutico. [**Clinical and Therapeutic Study of** *S. mansoni.*] *Brasil-Medico.* 1943, Aug. 21–28, v. 57, Nos. 34–35, 348–53, 20 figs.

BREBNER, I. W. **A Case of Hydatid Cyst of the Lung.** *South African Med. J.* 1943, Oct. 23, v. 17, No. 20, 319–20.

CANÇADO, J. R. Incidência da estrongiloidiase à tubagem duodenal. [**Incidence of Strongyloides in Duodenal Contents.**] *Brasil-Medico.* 1943, Sept. 4–11, v. 57, Nos. 36–37, 370–71, 4 figs.

Cançado has previously reported an incidence of Strongyloides infection of 8·6 per cent., on the basis of examinations of faeces at the Laboratoria Carlos Chagas, Bello Horizonte [see also this *Bulletin*, 1942, v. 39, 5, where the incidence is given as 8·2 per cent.]. He has now examined the duodenal contents of 1,142 persons and found larvae of *S. stercoralis* in 103 (9 per cent.). The infection is more common in the poorer people. *Charles Wilcocks.*

OLIVER-GONZÁLEZ, J. **Antigenic Analysis of the Isolated Tissues and Body Fluids of the Roundworm,** *Ascaris lumbricoides* **var.** *suum.* *J. Infect. Dis.* 1943, May–June, v. 72, No. 3, 202–12, 9 figs. [16 refs.]

The author begins with a brief summary of earlier work which has shown that antibodies appear in animals infested with Ascaris or

artificially immunized to it with extracts of the adult whole worm or of its isolated tissues. Marked tissue specificity was found by these workers; antibodies, produced in rabbits by injections of suspensions of Ascaris cuticle, muscle and so on, reacted at the highest titre to the homologous tissue. In this paper the author undertakes a more detailed study of the antibody nature of acquired immunity to Ascaris [*cf.* also WRIGHT and OLIVER-GONZALEZ below]. He also seeks to determine which of the antibodies in isolated Ascaris tissues are involved in the stimulation of antiparasitic factors in the host.

The methods used for the preparation of these tissue antigens are described. Precipitin disk tests were done with undiluted sera of infested rabbits overlaid with antigens at dilutions of 1 : 500 to 1 : 21,000. Living larvae of Ascaris, immersed in these rabbit sera, were incubated at 37°C. in vaselined hanging drops and the effect of the sera upon them was observed.

For details of the results the paper must be consulted. In general, the author found that sera of rabbits infested with Ascaris eggs or injected with extracts of powdered whole *Ascaris lumbricoides* of the pig caused precipitates round the mouth, anus, excretory pore, and cuticle of the larvae immersed in them [*cf.* TALIAFERRO and SARLES, this *Bulletin*, 1943, v. 40, 319]. Excellent photographs of these larvae are given. These precipitates began to appear about 24 hours after the larvae were immersed in these sera; these sera also immobilized and killed a large percentage of larvae (71 per cent. of 500 larvae in one series of experiments). Normal sera did not have these effects. Superinfection did not increase the effect on the larvae and it did not increase the precipitin content of the serum. The larvae were obtained from the lungs of guineapigs infested with *Ascaris lumbricoides* of the pig and the author recognizes that in this host the pig Ascaris does not develop further than the larval stage in the lung; but he suggests that the reason why it does not complete the intestinal stages is that antibodies immobilize and kill the larvae in the lung, where macrophages destroy them.

When rabbits were injected with extracts of isolated tissues of Ascaris (egg, muscle, cuticle, intestine, sperm, coelomic fluid), the anti-egg sera of these rabbits were the only ones which immobilized and killed the larvae immersed in them and caused precipitates at the mouth, anus excretory pore and round the cuticle. The anti-egg antibody was the most important of these isolated tissue antibodies, It and the anti-cuticle antibody produced the highest precipitin titres. The anti-egg antibody was still present in the sera 126 days after infestation; the other isolated tissue antibodies disappeared from the sera on about the 44th day after infestation. This may explain the presence of precipitins, in non-infected individuals, which has been reported by many workers; and it is possible that extracts of Ascaris cuticle, muscle, intestine, etc., are more reliable in diagnosing actual present infection than extracts of the whole worm.

Antibodies to all the tissue antigens also appeared in the sera of rabbits artificially immunized with extracts of whole worm, but each tissue antigen absorbed only its homologous antibody. This confirms earlier work.

The author discusses the part played by specific antibodies in acquired immunity to Ascaris and compares his results with those obtained by others who have used Ascaris, *Trichinella spiralis*, *Nippostrongylus muris*, *Ancylostoma caninum* and *Strongyloides ratti*. *G. Lapage.*

WRIGHT, G. G. & OLIVER-GONZÁLEZ, J. **Electrophoretic Studies on Antibodies to *Trichinella spiralis* in the Rabbit.** *J. Infect. Dis.* 1943, May–June, v. 72, No. 3, 242–5. [17 refs.]

Earlier work by OLIVER-GONZÁLEZ [*J. Infect. Dis.*, 1941, v. 69, 254; referred to by title in this *Bulletin*, 1942, v. 39, 627] indicated that the infestation of rabbits with *Trichinella spiralis* produces in their sera two types of antibody. The antiadult type affects the adult worms *in vitro* and partially protects rats against the intestinal stage of infestation; it appears about the 15th day after infestation, is lost by the 50th day, but reappears and reaches its highest titre after repeated infestations. The antilarval antibody gives no protection against the intestinal infestation and is not increased by repeated infestations.

This paper describes the authors' studies of rabbit antibody to Trichinella by electrophoretic methods. "Rabbits infected with *Trichinella spiralis* showed an increase in the proportion of gamma globulin in their serums as immunity to the infestation developed. The increase was not maintained by superinfection. Antibodies both against the larvae and against the adults were demonstrated in the gamma globulin, but not in the other electrophoretic components of these serums." *G. Lapage.*

MELCHER, L. R. **An Antigenic Analysis of *Trichinella spiralis*.** *J. Infect. Dis.* 1943, July–Aug., v. 73, No. 1, 31–9, 2 figs. [31 refs.]

The author set out to isolate and identify the chemical fractions of larvae (not adults) of *Trichinella spiralis*, which are immunologically active.

After a brief survey of the methods and results of earlier workers, the author describes his methods of obtaining larvae more suitable for this work than those used by these workers. Larvae digested out of hog's muscle were repeatedly washed in sterile saline until the negative biuret tests obtained from the washings indicated that the larvae were free from host protein. The larvae were then dried in the frozen state to prevent autolytic changes and were lyophilized to facilitate rapid and thorough extraction with lipoid solvents. "Proteins in a lyophilized state are much less subject to denaturation," so that their antigenic structure is less likely to be altered.

For the methods used for the isolation of the six chemical fractions used the paper itself must be consulted. These fractions were: (1) polysaccharide, (2) lipoid, (3) defatted insoluble residue, *p*H 8·3, (4) alkaline extract, (5) acid-insoluble protein, (6) acid-soluble protein.

Precipitin tests were done with four of these fractions and the sera of rabbits artificially infected with *Trichinella spiralis*. The lipoid fraction and defatted residue could not be used because they were insoluble in saline. These tests showed that the polysaccharide and acid-soluble protein are the potent precipitating antigens. The acid-insoluble protein gave no precipitate; the alkaline extract is merely an earlier stage of the acid-soluble fraction and contains also acid-insoluble and polysaccharide fractions. Probably for this reason its titre was lower.

Skin tests done with all the six fractions on the same rabbits 35 days after infection, indicated that these were of the delayed type, appearing 24 hours after injection of 0·1 ml. of antigen; they were

positive only with the acid-soluble fraction and the alkaline extract; again the alkaline extract showed a lower titre. No reactions occurred with the acid-insoluble and polysaccharide fractions; the lipoid and defatted residue fractions gave non-specific reactions with both infected and normal rabbits.

Precipitin tests with the sera of rabbits immunized with the polysaccharide and acid-soluble protein fractions and the alkaline extract and with alkaline extract of lyophilized powdered *adult pig Ascaris* showed that, with their homologous sera, the acid-soluble protein fraction gave a positive reaction at a dilution of 1 : 128,000, the polysaccharide at a dilution of 1 : 64,000 and the alkaline extract at a dilution of 1 : 20,000. The Ascaris alkaline extract reacted at 1 : 25,600, but there was no evidence of a common antigen between adult Ascaris and Trichinella larvae as stated by BARON and BRUNNER [this *Bulletin*, 1943, v. 40, 477].

The results indicate that the acid-soluble protein fraction is the one responsible for positive skin and precipitin reactions which earlier workers, using less refined extracts of larvae, regarded as valuable for the diagnosis of trichiniasis. This is a complete antigen. Its electrophoretic pattern was found to show only three components at the *p*H and ionic composition of the phosphate buffer used. The extremely slow mobility of the slowest component suggests that it may be a polysaccharide. *G. Lapage.*

DEFICIENCY DISEASES.

FOX, F. W. **Some Nutritional Problems amongst the Bantu in South Africa.** Reprinted from *Primeiro Cong. Méd. de Lourenço Marques.* 1938, Sept. 12, v. 3, 93–114. [14 refs.] [Summary appears also in *Bulletin of Hygiene.*]

The majority of the Bantu population in South Africa live in rural areas. In the past their diet was very simple, consisting of maize, milk, wild spinach, meat and Kaffir beer, and the author demonstrates clearly that with these foods the natives were able to enjoy a diet of high nutritive value. Comparatively small changes, however, are capable of bringing about serious deficiencies in diets as simple as this because each food contributes some dietary factor absent from the others. Destructive methods of farming, and contact with Western civilization, are revolutionizing the food habits of the Bantu people, and the outcome seems likely to be disastrous. The maize crops are becoming smaller and smaller every year, yet the natives sell their crops for cash as soon as they are reaped, only to buy them back again later during a time of shortage for as much as three times their original price. The first and most urgent need seems to be for an adequate supply of imported grain at reasonable prices. There is also a great decrease in the amount of milk available, owing to steady deterioration of the grazing. For the same reason meat is becoming more and more scarce, and possibly Kaffir beer is the only food which is still being made and used in these areas just as it was in former days.

Besides the diet becoming worse because of deterioration of the land, the more sophisticated natives are drifting steadily in the direction of imported foods such as refined mealie meal, white bread and sugar. The change is being hastened by a widespread advertising campaign.

There seems to be a general agreement that, while the people exhibit a remarkable power of adjustment, enabling them to survive periods of famine and starvation, their physique is gradually deteriorating. Mortality is high in early life, 15–25 per cent. of the children die during the first year, 25–38 per cent. before reaching two years, and 30–60 per cent. before they are 18. [See also this *Bulletin*, 1943, v. 40, 865.]

E. M. Widdowson.

VENOMS AND ANTIVENENES.

MACHT, D. I. **Comparison of Effects of Cobra Venom and Morphine on Unanesthetized Cat.** *Proc. Soc. Exper. Biol. & Med.* 1943, June, v. 53, No. 2, 225–7, 3 figs.

The effects of morphine on the brain and neuro-muscular activity and on the pupil are, in the case of felines, the opposite of what occurs in man. It excites the brain of cats in proportion to the dose and dilates the pupils. Since morphine and cobra venom are both used as analgesics the author thought it would be interesting to compare them in their actions on unanaesthetized cats. He used a cobra venom free from haemotoxic and cytotoxic principles and from protein, in other words cobra neurotoxin.

First, as regards general behaviour. Whereas morphine induced excitement increasing with the dose, cobra venom in small doses, 5–10 mouse units per kgm. had no obvious effect beyond producing a mild euphoria (as with catnip); larger doses, 10–20 units, were sedative, producing drowsiness, and 40 units were depressant and caused tremor and unsteady gait. In short, the effects of cobra venom were the reverse of those due to morphine.

Secondly, effects on the pupils. In cats, small doses of morphine (1 mgm. per kgm.) produced mydriasis and larger doses greater dilatation and failure to react to light. Cobra venom in small doses of 5 m.u. had no effect; larger, such as 5–20 m.u. caused myosis, starting in an hour and persisting up to 24 hours.

Myosis in man, resulting from morphine, is due, it is believed, to central action and increase of oculomotor tone. Local application of venom had no effect on the iris of the cat's intact eye, but the negative results of experiments on isolated iris muscle *in vitro* showed that the myosis effects of venom are central in origin, and when the cats were decerebrated by severing the upper brain just below the thalamus, leaving the oculomotor nuclei intact, cobra venom when injected narrowed the pupils. The sequence of events may be illustrated by one example.

Morphine.—A cat weighing 2·3 kgm. had pupils 2–3 mm. in width at noon before experimentation. At 12.15 p.m. 30 mgm. of morphine sulphate were injected intramuscularly. At 12.40 p.m., animal very restless and excited, pupils circular, maximal dilatation. The excitation continued and quiet was not restored till next day and the pupils were still dilated but becoming smaller, 6 mm. in diameter.

Cobra venom.—Cat weighing 2·8 kgm.; pupils 5 mm. at noon. At 12.10 p.m. 30 m.u. venom injected; at 12.40 p.m. animal quiet, pupils

same width; 2 p.m. pupils 2 mm., at 3 p.m. 1–2 mm. and animal somnolent. Next day the behaviour was normal and pupils were dilating again, 3 mm., but not yet back to normal size.

H. Harold Scott.

KHAN, F. K. **Evaluation of Sodium Bisulphite and Ascorbic Acid as Antidotes of Cobra Venom.** *J. Indian Med. Ass.* 1943, Aug., v. 12, No. 11, 313.

GHOSH, DE and CHAUDHURI [this *Bulletin*, 1942, v. 39, 405] found that reducing agents such as sodium bisulphite and ascorbic acid, when mixed with cobra venom *in vitro*, were capable of effecting considerable reduction of toxicity. The author has investigated the use of these substances in the treatment of experimental injection of cobra venom. Of the specimen of venom used, the smallest dose which was always fatal to dogs was found to be 0·6 mgm. per kgm., and this dose was injected intramuscularly. Sodium sulphite, or ascorbic acid, in doses of 0·5 to 1·0 gm. was injected intravenously 5–10 minutes after the injection of the venom. All the dogs died with the usual symptoms of cobra poisoning, and after the usual interval. This form of treatment appears, therefore, to give no sign of usefulness. *Charles Wilcocks.*

DE MAGALHÃES, O. & GUIMARÃES, R. Escorpionismo—Alguns dados estatisticos e observações de acidentes. [**Scorpion Sting. Statistical and other Data.**] *Mem. Inst. Biol. Ezequiel Dias.* Belo Horizonte. 1939 & 1940, v. 3 & 4, 137–94, 5 figs. on 4 pls.

The authors refer, in passing, to previous records they made on the subject of scorpion stings in 1929, but say that the present article is of much greater importance because the number of cases on which their observations are based is much greater (107 in the former, 2,449 in the present), the intraspinal method of administration of antivenene has proved vastly superior to the subcutaneous and intravenous routes and much less of the serum is needed.

Cases of scorpion sting in Belo Horizonte are commonest in the month of October, as the following table for the two years 1939 and 1940 shows:—

Month	1939	1940	Total
January	46	57	103
February	39	43	82
March	39	52	91
April	25	52	77
May	43	45	88
June	26	48	74
July	40	52	92
August	28	58	86
September	54	86	140
October	88	126	214
November	42	95	137
December	60	84	144
	530	798	1,328

[The totals given in the tables throughout this article are more often wrong than right, a fact which engenders some doubt as to the correctness of the constituent figures, as these cannot be checked.]

The majority of the victims were young children living most of the time in or around the house, where the scorpions hide, and playing in the passages and gardens; the scorpions lurk in the ivy on the walls and one of the prophylactic measures proposed is destruction of the ivy. The sting is not often fatal except in the young, but in this series there were 145 deaths; of the fatal cases only 37 had received antiserum and some of these were patients almost moribund when it was given and others received it several hours after the accident. The authors regard 20 of the 37 as "wrongly interpreted as failures of serum."

The poison acts on the nervous system and kills by its effect on the cardiac and respiratory centres in the bulb; death may take place even within half-an-hour. Much of the paper is given up to description of the symptoms in individual patients; one may be detailed as typical of a case ending fatally.

A boy of 2 years was stung on the finger by an adult *Tityus serratulus* at 3.30 p.m. He was seen a quarter of an hour later and was given 30 cc. antiserum intramuscularly and subcutaneously [although in their opening statements the authors stress the much better success resulting from the intraspinal administration], and 10 cc. more at 5 p.m. The child had a slight cough, marked rapidity of respiration, rhinorrhoea and frothy expectoration; pulse 140, regular; marked prostration and vomiting, intense pain, distress, crying out at intervals, profuse sweating, generalized *cutis anserina*. Soon after 5 p.m. the vomiting ceased, but the patient was livid and cold for some little time longer; then warmth returned, but at 11 p.m. the agitation and distress became very great and thirst intense; 20 cc. antivenene given. Sweating ceased, dyspnoea severe, pupils dilated, general tremors, restlessness; at 2.30 a.m. marked delirium, meningismus, rigidity of limbs and neck, nystagmus; became quieter and died at 3 a.m., less than twelve hours after the accident.

H. Harold Scott.

SMITHERS, R. H. N. **The Distribution of the "Knopiespinnekop"** (*Latrodectus indistinctus*). *South African Med. J.* 1943, Sept. 25, v. 17, No. 18, 293, 1 map.

Smithers has published a map showing the distribution of *Latrodectus indistinctus* and of its variety *karooensis* in the Cape Province of South Africa. He mentions the success which has attended treatment of persons bitten by the former by means of antivenene prepared by the Union Health Department. *Charles Wilcocks.*

EAST AFRICAN MED. J. 1942, Nov., v. 19, No. 8, 262–3. **Two Fatal Cases of Bee-Stings.**

Two Indian boys were attacked by bees at 5.15 p.m., and were admitted to Dodoma Hospital, Tanganyika Territory, at 7.15 p.m. and seen by the doctor at 8 p.m. They had been stung all over, one boy having 400 stings on the face, head and neck alone. Both were in a state of profound shock with feeble heart sounds, rapid pulse, cold limbs and subnormal temperature. The skin was much swollen, especially on the face. Treatment for shock was given immediately but the

patients gradually became comatose and died next morning at 8 a.m. and 9 a.m., respectively. Permission for autopsy was not obtained.

J. F. Corson.

DERMATOLOGY AND FUNGOUS DISEASES.

LIVINGOOD, C. S., ROGERS, A. M. & FITZ-HUGH, T., Jr. **Dhobie Mark Dermatitis.** *J. Amer. Med. Ass.* 1943, Sept. 4, v. 123, No. 1, 23–6, 5 figs.

[A careful study throwing light on one at least of the conditions hitherto grouped under the term "Dhobies' itch." There is a general tendency to class all epiphytic dermatitis in the tropics under this head and to blame the poor dhobie for introducing it.]

The authors have shown that a form of dermatitis venenata is commonly due to the use of a fluid from the nut of the ral or bella gutti tree [*Semecarpus anacardium*] with which the native washerman marks the clothes for laundering. At the 20th General Hospital 11 cases occurred among 55 officers and 41 among 344 men. All are not, therefore, equally susceptible. The symptoms caused are local pruritus in a few hours after contact, followed by dermatitis of varying degree from erythema to oedema, vesiculation, oozing and crust formation. In the cases seen by the authors the sites involved were the neck, waist-line, ankles, feet and lower third of the legs. The marking of the linen or socks is done by using the juice obtained by pushing a pin through the capsule of the nut to the brown or black fluid within. Such marks will withstand half-a-dozen washings or more. By patch tests it was shown that the juice from green nuts was much more potent than that from older and dried nuts; boiling the marked clothes will not remove the irritant, and in fact in sensitive persons appears to enhance the effect; exposure to sunlight and even to solvents such as ether, acetone, 95 per cent. alcohol, and "white gasoline" do not reduce the sensitizing properties. Fluids from different nuts vary greatly in potency, hence the varying incidence of cases among different dhobies' *clientèle.*

In their conclusions the authors state: "We believe it most unlikely that cutaneous fungous infections are transmitted by clothing washed by dhobies and therefore urge that the use of the term 'dhobie itch' as a synonym for tinea cruris and epidermophytosis be discontinued."

[Perhaps it is too soon to do away altogether with the term "dhobie itch," for though the authors have done good work in separating "ral nut dermatitis" from epiphytic conditions, they have not shown that *all* dhobie itch is due to this. Probably the commonest sites of dhobie itch are the crutch and the axillae and the parts of the linen coming into contact with these areas are not those where the dhobie puts his identification marks.]

H. Harold Scott.

[*Semecarpus anacardium* contains powerful vesicants and causes blistering within 12 hours; it is said to be used by malingerers in India. It is called *Chola gutti* in Assam and *Chela* in India. The word *ral* is a general term for several kinds of trees in India.—*Ed.*]

GOLDSMITH, N. R. **Dermatitis from Semecarpus Anacardium (Bhilawanol or the Marking Nut) spread by Contaminated Mail.** *J. Amer. Med. Ass.* 1943, Sept. 4, v. 123, No. 1, 27, 1 fig.

A bottle containing Bhilawanol Oil, the juice of the "marking nut tree," *Semecarpus anacardium*, in transit by post came unstoppered and other pieces of the mail were soiled with it. Sixteen employees who came in contact with the juice complained of itching and burning of the hands, arms and face, and developed a dermatitis of varying severity—a dermatitis venenata. Patch tests with the oil diluted 1 : 1,000 gave strongly positive reactions in 72 hours. The pericarp of the fruit of the tree contains a dark brown to black corrosive juice which is used for dyeing and for marking linen—hence the name [see above]. The juice has been found by analysis to contain a monohydroxyphenol (semecarpol), a dihydroxy compound, $C_{21}H_{32}O_2$ (bhilawanol), and a tarry corrosive residue, but no anacardic acid, cardol, catechol or anacardol.

H. Harold Scott.

LIEBERTHAL, E. P. **Pinta (Mal del Pinto, Carate) in Continental United States. Report of Three Cases with Late Manifestations and Review of the Salient Features of the Disease.** *J. Amer. Med. Ass.* 1943, Nov. 6, v. 123, No. 10, 619–24, 3 figs. [11 refs.]

An instructive article which might well constitute a clinical lecture on the subject of *mal del pinto*, with three typical illustrative cases. The author does not bring forward anything fresh, but stresses the differences which may be observed between Cuban and Mexican cases, especially the regularity and prominence of the cutaneous lesions, the punctate palmar and plantar hyperkeratoses. [It is perhaps a pity to speak so often of the "vitiligoid areas" of pinta, as the author does, since vitiligo is one of the most important of the conditions requiring to be differentiated from *mal del pinto* and the distinction is often quite definite, see this *Bulletin*, 1944, v. 41, 66.] *H. Harold Scott.*

JACOBSON, C. F., Jr. & DOCKERTY, M. B. **Blastomycosis of the Epididymis : Report of Four Cases.** *J. Urology.* 1943, Aug., v. 50, No. 2, 237–48, 5 figs.

Gilchrist's disease, caused by *Blastomyces dermatitidis*, occurs in two clinical forms : (1) a *cutaneous blastomycosis* tending to progress as a chronic or subacute ulcerative process responding well to iodide medication and irradiation ; and (2) a *systemic blastomycosis* involving the viscera, especially the lungs, and tending to a fatal issue. The systemic form may be primary or may develop by extension from the cutaneous form.

The authors describe four cases of the disease with involvement of the epididymis, a complication sufficiently unusual to merit special report. The cases are dealt with mainly from the viewpoint of the genito-urinary surgeon, and the diagnosis was based on the discovery of the causative fungus in sections of the lesions in the epididymis. No reference is made to isolation of the fungus in culture. In all four cases the skin was involved, the common lesion being a subcutaneous nodule, painless at first, which broke down and ulcerated on the surface leaving a discharging sinus. In three of the patients the skin lesions were generalized over the body, and in the other localized to the face.

In all cases the skin lesions yielded to intensive potassium iodide medication by the mouth and local X-ray and ultraviolet ray therapy; but despite the improvement in the skin lesions, the epididymal and, probably, other visceral lesions tended to progress even during treatment. On cessation of the treatment, before cure, new skin lesions quickly developed. One patient was definitely cured, but two died. At autopsy it was found that one had primary cutaneous blastomycosis with subsequent extension to the viscera, but not the lungs; the other had primary pulmonary blastomycosis of some duration, which became generalized in the viscera and skin and assumed an acute fulminating character. The remaining two cases may have been primary pulmonary infections. *J. T. Duncan.*

COSTA, O. G. Esporotricose no Brasil. [**Sporotrichosis in Brazil.**] *Brasil-Medico.* 1943, Aug. 21–28, v. 57, Nos. 34–35, 343–7. [111 refs.]

PIMENTEL IMBERT, M. F. Broncomoniliasis. Reporte de un caso fatal. [**A Fatal Case of Bronchomoniliasis.**] *Rev. Med. Trop. y Parasit.* 1943, Mar.–Apr., v. 9, No. 2, 16–18.

Bronchomoniliasis is usually regarded as an accidental or incidental affection of the respiratory tract in which the sputum contains *Monilia albicans*; it causes little or no constitutional disturbance and clears up spontaneously. At times, as in the case described here by the author, the condition may be grave and even fatal, after symptoms of fever, sweats, pain in the chest and cough with mucopurulent sputum, perhaps blood-stained, accompanied by dyspnoea and cyanosis.

The present case, the first in Santo Domingo, occurred in a negro, 39 years of age, a cook by occupation, who had lived in the district for 12 months.

On admission to hospital he gave a history of high fever, shivering, vomiting, intense headache and general pains. His condition was obviously serious; he was of an ashy grey colour, the sclerotics were jaundiced slightly, there were scattered râles in the lungs, the liver was enlarged to two fingers'-breadths below the costal margin and the glands of the neck and groin were enlarged. Blood examination showed red cells 4,030,000 per cmm., haemoglobin 75 per cent., leucocytes 22,500 (83 per cent. polymorphonuclears, 7 per cent. lymphocytes and 10 per cent. monocytes). A fortnight later the red cells were about the same, 4,020,000, white 15,250 per cmm. and 93 per cent. polymorphonuclears. Sputum showed abundant Monilia and growth was obtained on Sabouraud's medium and the patient's serum agglutinated it up to 1 : 640. During his time in hospital the temperature ranged between 36·7° and 40·8°C. and the pulse between 72 and 150, respirations 26 to 70 a minute. The sputum was thick, tenacious muco-pus, never containing blood. Death took place 17 days after his coming to hospital. Treatment consisted of urotropine and sodium salicylate in small doses, then digitalis and lastly sodium iodide "too late and in inadequate doses."

Autopsy revealed trachea and bronchi red and oedematous and containing blood-stained fluid; the lungs were voluminous and congested and exuded bloody serum on section; the pleura were thickened and adherent. Monilia was isolated from the exuding serum.

H. Harold Scott.

PERRÍN, T. G. & MARTÍNEZ BÁEZ, M. Nota sobre el primer caso de histoplasmosis en Mexico. [**First Case of Histoplasmosis in Mexico.**] *Rev. Inst. Salubridad y Enfermedades Trop.* Mexico. 1943, Mar., v. 4, No. 1, 79–87, 10 figs. on 5 pls. [21 refs.]

Recent observations having shown that histoplasmosis is a more common disease than has been suspected hitherto, the authors have been led to place on record the details of a case which was presented by them before the National Academy of Medicine of Mexico in 1937. The case, a fatal one, was in a man 68 years of age who suffered from ulcerative pharyngitis and bronchitis. Material from the pharynx was removed by biopsy and in preparations made from it *Histoplasma capsulatum* was discovered. The organism was also found in sputum from the lungs and in cells in the urinary deposit. There being no specific remedy for the disease, various drugs were tried in vain. The infection was evidently generalized, as evidenced by the pharyngeal and pulmonary condition and the cystitis. *C. M. Wenyon.*

MISCELLANEOUS.

COLONIAL OFFICE. **Colonial Research Committee. Progress Report 1942–1943** [HAILEY, Chairman]. Cmd. 6486. 26 pp. 1943. London: H.M. Stationery Office. [6*d.*]

BULL. INST. HYG. MAROC. 1942, v. 2, 91–142. Rapport sur l'activité des Services de la Direction de la Santé, de la famille et de la jeunesse pendant l'année 1942. [**Report on the Health Services of Morocco during the Year 1942.**]

Medical and sanitary work during 1942 was much handicapped by shortage of staff, equipment and transport owing to the war. The staff included 251 doctors and 149 European nurses as well as some hundreds of trained native assistants. The population of Morocco, about 6½ millions, is composed of Mohammedans, Jews and Europeans.

The diseases recorded in out-patients and in-patients are grouped as injuries (30–40 per cent.), fevers (40–50 per cent.) and venereal diseases (nearly 20 per cent.).

Infectious and contagious diseases.—The increase in these diseases is attributed to overcrowding, less and poorer food, lack of soap and difficulties in carrying out town sanitation. The deaths from infectious and parasitic diseases have more than doubled since 1940, the chief cause being an outbreak of typhus fever. *Malaria* is widespread and in 1941 there was a serious epidemic in the Atlantic coastal regions. *Typhus fever* [of the classical louse-borne type] increased in incidence from 1,666 cases in 1941 to 28,802 in 1942; 556 were in Europeans. Other infectious diseases were less prominent: *smallpox*, 2,078 cases, including about 50 Europeans; *rubella*, 1,254; *scarlet fever*, 64; *diphtheria*, 359, mostly mild cases; *cerebrospinal meningitis*, 20. The figures for *tuberculosis* are unreliable, diagnosis being mainly clinical: 7,951 cases are recorded with 2,676 deaths, 124 deaths being in Europeans. About 77,000 cases of *trachoma* were diagnosed, the greatest prevalence being at Marrakesh. There were 976 cases of *rabies* in natives and 611 in Europeans; nearly all were caused by

dog-bites, usually by stray dogs, but cats (96), donkeys (45), cattle (21), horses and mules (14), rats, pigs, camels, a rabbit, and man (10) also transmitted it. *Syphilis* was the chief venereal disease, 20,000 cases being diagnosed. Among 25,000 cases of *dysentery* less than 100 were bacillary.

Special prophylactic measures.—Malaria: Prophylactic measures were continued but were hampered by shortage of drugs and larvicides and lack of transport. *Venereal diseases*: brothels are inspected; 20,000 women were treated during the year. *Smallpox*: over 500,000 vaccinations were done. *Plague*: there was a decrease in incidence from 2,337 in 1941 to 583 in 1942; as prophylactic measures, 80,000 vaccinations were done and over 60,000 rats were caught.

Other activities recorded in the report are Port Hygiene, various charitable undertakings, and building work, projected and accomplished.

J. F. Corson.

SCOTT, H. H. **The Influence of the Slave-Trade in the Spread of Tropical Disease.** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1943, Dec., v. 37, No. 3, 169–88, 7 figs. on 1 pl.

In this Presidential Address to the Royal Society of Tropical Medicine and Hygiene, Sir Harold Scott has taken a subject peculiarly his own, as readers of his *History of Tropical Medicine* will know. He deals with the slave trade in relation to the spread of disease, and the paper bears evidence of the wide historical research he has undertaken. After a general account of the slave trade he discusses yellow fever, considering at length the question of the origin of this disease, whether in the Old World or in the New. On the whole he inclines to the view that Africa was its original home, and that it spread thence to America. Leprosy was probably introduced into America by the Spaniards and Portuguese, but there can be little doubt that the influx of slaves from the heavily infected peoples of tropical Africa contributed largely to the prevalence of the disease in the Americas. Yaws was probably present in the West before the days of Columbus, but during the period of slave trading fresh cases must constantly have been brought from Africa.

African trypanosomiasis is in a different category, depending as it does on cyclical development of the trypanosomes in Glossina. These flies are not found in America, and though patients with negro lethargy were carried there, no extension could take place. Dengue may have been transported from Africa to Guadeloupe; there is some reason to think that the outbreak of *coup de barre* in 1635 was an outbreak of dengue.

Of the helminthic infections, nothing is certainly known of the origin of *Wuchereria bancrofti*, but it is more than likely that *Acanthocheilonema perstans* and *Loa loa* were carried from Africa to America, and that the slave trade played a great part in this transfer. It seems to be accepted that *Dracunculus medinensis* and *Schistosoma mansoni* were similarly carried to and fostered in America.

Finally, the ackee, *Blighia sapida*, is a tree indigenous to West Africa, which was carried to Jamaica in a slave ship in 1778. [Readers will remember that it is to Sir Harold Scott that the credit for relating the highly fatal vomiting sickness of Jamaica to the eating of the unripe fruit of this plant is chiefly due.]

[The address betrays the wide interests of an enquiring mind; its subject is not remote from present-day problems, for the massive and

rapid movements of large numbers of people about the world, as a result of war, may bring results not unlike those of the slave trade, in relation to the spread of disease.] *Charles Wilcocks.*

i. CHARTERS, A. D. **The Causation of Tropical Ulcer.** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1943, Dec., v. 37, No. 3, 205–15. [16 refs.]

ii. BUCHANAN, J. A. C. [**Tropical Ulcers in association with Food Deficiency.**] [Correspondence.] *East African Med. J.* 1943, Nov., v. 20, No. 11, 394.

i. Among many conditions which have been thought to cause tropical ulcer the author finds, from a review of some of the literature, that there is a good deal of evidence in favour of dietary deficiency being responsible.

The distribution of cases of tropical ulcer among African troops who were admitted to an East African hospital was remarkable; during the period from November 20th, 1942, to May 20th, 1943, out of 570 East Africans there was one case of tropical ulcer and that case was doubtful, while among 292 Somalis there were 1·43 cases. All were living under the same conditions except in regard to diet; that of the Somalis was relatively and actually deficient in vitamin A and riboflavin while both diets were deficient in calcium.

Tests were therefore made by giving calcium, cod liver oil (vitamin A) or condensed milk (riboflavin) to different groups of patients receiving the Somali diet. Other groups were given coramine (as a substitute for nicotinic acid) and ascorbic acid respectively. The only local treatment was a dry dressing applied twice a day. The ulcers were measured every three days.

It was found that the greatest and quickest improvement occurred in those receiving calcium, cod liver oil, and condensed milk. A trial of campolon on another patient eliminated riboflavin as a cause of the improvement and it was concluded that the good effect of the condensed milk was due to its calcium. To discriminate between vitamins A and D in the cod liver oil, 55 patients were given peprika (sweet pepper) which is rich in carotene; 52 (94 per cent.) improved.

Since the diet of the East Africans also contained little calcium the tests suggested that a deficiency of vitamin A was the cause of the ulcers in the Somalis; moreover, the disease did not attack Somalis of one unit whose diet included ghee substitute, containing 3,500 I.U. of vitamin A per ounce; the patients, however, showed none of the classical signs of vitamin A deficiency such as Bitot's spots, xerophthalmia, hemeralopia or phrynodermia. The deficiency theory does not conflict with that of infection, as deficiency may predispose to infection. The author recommends the addition of ⅛ oz. of peprika to the daily diet; alternatives are green chilli, lettuce, watercress, and spinach. [Red palm oil, rich in vitamin A, might also be used, where available, see this *Bulletin*, 1943, v. 40, 331. For an account of beriberi among Somali troops, *ibid.*, 1943, v. 40, 856.]

ii. The writer comments on a reference by ANDERSON [*Bulletin of Hygiene*, 1944, v. 19, 138, to the occurrence of tropical ulcers among these troops. Buchanan points out that the East African troops wore boots and puttees while the Somalis wore sandals only until puttees and socks were issued to them to protect their legs and ankles. He closely investigated these cases and became convinced that trauma as a direct

cause of the ulcers could not be discounted, though a change from their natural diet was no doubt a predisposing cause. He also states that calcium in the form of bone-meal was not, in fact, added to the East African native diet in this northern command. [The last statement is confirmed in an editorial note.] *J. F. Corson.*

KELLERT, E. **Rhinoscleroma. Report of a Case.** *New England J. of Med.* 1943, Oct. 21, v. 229, No. 17, 647–50, 5 figs. [11 refs.]

Rhinoscleroma is rarely seen in the United States; the few cases have mostly occurred in foreign-born persons. It is, however, becoming more often recognized owing to more frequent biopsy and improved diagnosis. The patient whose case is described in this paper was a Pole, aged 66 years, who had lived in Massachusetts for many years. When first seen in 1928 he showed a tender, but not painful, granular, indurated lesion of the hard and soft palate, with greyish areas, apparently cicatrices. The uvula was absent. The post-pharyngeal wall was involved. The palate and contiguous buccal mucosa were very hard (suggesting scirrhous carcinoma) and bled freely on manipulation. The nose was not involved, though there was a foul discharge from the nostrils. Biopsy specimens revealed typical changes.

The patient was not seen again till 11 years later, in 1939. On account of difficulty of breathing he had had a tracheotomy done some months before. The oral cavity had contracted from the cicatrized palate being drawn towards the base of the tongue; the tonsils could not be seen. A second biopsy revealed changes similar to those of the first. Death occurred about 20 years after the symptoms first appeared. Permission for autopsy was refused. *Klebsiella rhinoscleromatis* was grown on both occasions and the original culture had retained its characteristics over a period of 14 years. *H. Harold Scott.*

EADS, J. T. & KASH, R. M. **Favism. Report of a Case.** *U.S. Nav. Med. Bull.* 1943, Nov., v. 41, No. 6, 1720–24.

A general account of favism with description of a typical case of a fairly severe attack in a private of the U.S.A., of Spanish stock and aged 31 years. His symptoms were quite characteristic: headache and general pains, chills, moderate rise of temperature (101°F.) and haemoglobinuria, with nausea, vomiting, jaundice, anaemia and asthenia. Treatment comprised epinephrin at the onset to combat the dyspnoea, sense of oppression in the chest and collapse, transfusion of whole blood, 3,000 cc. in the first week, and of plasma 500 cc. during the phase of shock, 5 per cent. dextrose intravenously freely during the first few days, liver extract intramuscularly and later iron in large doses.

The important point in diagnosis is to bear the possibility in mind. The condition is very rare in the United States but should be constantly thought of by medical men serving in the Mediterranean. The rarity in the United States and other countries is ascribable to the fact that there does not seem to be any species of Vicia native to those countries, but as *V. fava* is, the authors state, now being cultivated in the States more cases are likely to be encountered. [See also this *Bulletin*, 1942, v. 39, 279, 639.] *H. Harold Scott.*

CLELAND, J. B. **Plants, including Fungi, Poisonous or otherwise Injurious to Man in Australia.** *Med. J. Australia.* 1943, Aug. 28, v. 2, No. 9, 161–4. [15 refs.]

HUFFAKER, C. B. & BACK, R. C. **A Study of Methods of Sampling Mosquito Populations.** *J. Econom. Entom.* 1943, Aug., v. 36, No. 4, 561–9. [11 refs.]

In order that mosquito control measures may be intelligently directed it is desirable to know the relative abundance of various species in the adult population. Most of the methods employed for sampling the natural populations have been criticized on the ground that they do not give representative samples.

One of the most popular devices for catching mosquitoes is the New Jersey mosquito trap, but it is pointed out that owing to the complex behaviour patterns of mosquitoes it is unlikely that any one apparatus can present conditions equally attractive to all the prevailing species. The traps usually contain a source of light and carbon dioxide as attractants, and a fan. By using each of these alone and in various combinations, and by comparing the catches so obtained with each other and with the results of other methods (*e.g.*, counts of mosquitoes attempting to feed, sweeping the air at intervals, insects resting in barns and barrels) it was thought that it might be possible to develop a correction factor which could be applied to the results of the New Jersey trap catches so that a more accurate picture of the relative numbers of different species occurring naturally could be obtained.

The percentages of some 20 species caught by the different methods show striking divergences. For example, *Anopheles quadrimaculatus* varied from 8·4 per cent. in traps with light and carbon dioxide, to 20 per cent. in air sweepings and to over 90 per cent. in barns and barrels.

Inspection of the results led to the conclusion that traps containing various combinations of light and carbon dioxide showed differences in their relative attractiveness to species according to prevailing conditions. That is to say, the contrast between the condition presented by the trap and those of the surroundings is important. Isolated traps with no attractants collect the most representative samples but in numbers too small to provide data for correction factors except when the population density is very high. However, correction factors for several species are presented: these are obtained by determining the relative percentages of several species recorded for the trap without attractants and, say, with a source of light. From these two values the error introduced by the use of the slight attractant is easily estimated and the factor devised is used for correcting future results.

W. A. L. David.

REBÊLO, A. & DE CARVALHO PEREIRA, Mario. Estação anti-malárica de Lourenço Marques. Culicini (Diptera, Nematocera) da colónia de Moçambique. [**The Culicines of Mozambique.**] Reprinted from *Moçambique.* 1943, Apr.–June, No. 34, 81–90, 1 fig.

OVIEDO BUSTOS, J. M. **Coccidiosis in Human Subjects (Isospora bigeminum).** *Arch. Argentinos Enferm. Aparato Digest. y Nutric.* Buenos Aires. 1943, Feb.–Mar., v. 18, 246. [Summary taken from *J. Amer. Med. Ass.* 1943, Oct. 16, v. 123, No. 7, 446.]

According to Oviedo Bustos, Isospora hominis and Isospora bigeminum are the two genera of coccidia which are parasitic for human subjects. Isospora bigeminum was encountered in the two cases described by him. While the majority of cases reported in the literature originated in the Eastern Mediterranean and in Japan, China and

India, cases also have been reported from several parts of Argentina. Excreta of animals are presumably the cause. The symptomatology of coccidiosis, which is chiefly of the gastrohepatic and rectocolonic type, is accompanied by allergic phenomena. There may be dyspepsia and hepatic colics, constipation or diarrhea, flatulence, rectal tenesmus, anal pruritus and spasticity of the colon. The allergic phenomena are a generalized pruritus, erythema, urticaria, edema of the eyelids, rhinitis, asthmatic bronchitis and eosinophilia. The treatment is antiparasitic. Emetine, acetarsone, chiniofon and gentian violet are recommended. According to the experiences of Becker, vitamin B_1 and B_6 should be added. The author's observations indicate that Isospora bigeminum is difficult to eradicate.

JOHNSON, R. E. **Nutritional Standards for Men in Tropical Climates.** *Gastroenterology.* 1943, Sept., v. 1, No. 9, 832–40. [25 refs.]

Dietary needs are, in general, qualitatively similar in hot and in temperate climates. Quantitatively, however, the requirements for certain constituents may be altered in hot climates by increased losses in sweat, by anorexia and by the specific effects of heat. The prevention of heat stroke, heat dehydration and heat cramps—and the maintenance of efficient physical performance—offer a guide to the assessment of a number of food requirements. The author discusses, from these points of view, the provision of water, sodium chloride, calories and the vitamin B complex.

Water shortage, resulting in the exhaustion of dehydration, is very easily induced. To prevent the deficiency syndrome, and to ensure the best physical performance, men should always be maintained in water balance. Actual requirements depend on environmental conditions, on the degree of activity, and on individual idiosyncrasies in the rate of sweating.

Deficiency of sodium chloride will lead, after several days, to poor performance, will predispose to heat exhaustion and will later produce heat cramps. Exact requirements depend on surrounding conditions, on the degree of physical activity, and on the composition of the sweat. Sedentary men rarely need more than 10 gm. of salt a day, working men need 15–20 gm. Salt should be given in the drinking water, in a concentration not greater than 0·2 per cent. Salt tablets cause gastric distress and are not recommended. Excessive amounts of salt (over 40 gm. a day) are deprecated, as thirst is thereby increased and the work performance reduced.

Recent research has not confirmed earlier reports of considerable losses of water-soluble vitamins in the sweat, especially of thiamin and ascorbic acid. Of the vitamins, those of the B complex merit most attention, particularly in providing emergency rations for active subjects. It has been shown that men working in cool climates on a deficient diet can show signs of vitamin B deficiency in a week or two. The vitamin requirements for avoiding deficiency syndromes are the same in hot climates as in cooler conditions.

It has been found that fit men can carry out work satisfactorily in hot climates for a period of a week on a low calorie supply, losing body fat to the extent of 5–10 per cent. of the body weight, without ill-effects. This is of importance when issuing rations for short periods.

Palatability of the rations needs special attention in the tropics, since anorexia is so widespread. *J. S. Weiner.*

CAPLAN, A. **A Critical Analysis of Collapse in Underground Workers on the Kolar Gold Field.** *Bull. Inst. Mining & Metallurgy.* 1943, Nov., No. 463, 1–70, 12 figs. [15 refs.] [Summary appears also in *Bulletin of Hygiene.*]

All cases of alleged collapse in underground workers, however mild, during a period of two years were seen by the author on admission to hospital, usually one to two hours after the collapse. There were 293 cases in all, but in 49 of them there had been no collapse or it was not related to underground conditions. These 49 cases are analysed. The remaining 244 cases were assessed as due wholly or partly to underground conditions; and they comprise 194 cases in which the collapse was classed as "mild," 41 classed as "moderate," and 9 in which there was "severe" collapse.

The mild cases had almost completely recovered when admitted to hospital. They gave histories of fatigue, asthenia, giddiness, nausea and, less frequently, vomiting, cramp and loss of consciousness. Loss of consciousness was often momentary and was probably never of more than 10 minutes' duration. Abnormal physical signs noted were hypotension (systolic blood pressure 95 to 105 mm. Hg) in 37 per cent. of cases; reduced pulse pressure (5 to 15 mm. Hg) in 26 per cent. of cases; bradycardia (pulse rate 40 to 60) in 21 per cent.; low plasma chloride concentration (under 560 mgm. per cent.) in 67·7 per cent. of 170 blood examinations; and mild dehydration, as indicated by some loss of skin elasticity, in 9 per cent. of cases.

The "moderate" and "severe" cases gave a clinical picture resembling surgical shock. The arbitrary criteria for classification as "severe" were complete unconsciousness, and inability to palpate the pulse at the wrist. In both these groups of cases the prodromal symptoms of fatigue, asthenia, giddiness and nausea were always followed by vomiting, cramp and unconsciousness, with visual and aural disturbances in roughly half the cases. Vomiting often recurred five or six times; and the vomiting was followed within a few minutes by cramp of varying degrees of severity—usually confined to the extremities but sometimes affecting the abdomen and trunk. The skin was cold and clammy, the temperature as low as 95° to 96°F., the pulse weak or absent, and the heart rate 80 to 140 beats per minute. In severe cases the blood pressure was indeterminable; and in the moderate cases it was commonly 60 to 90 mm. Hg, and always below 95 mm. Pulse pressures were 2 to 10 mm. Haemoglobin estimations as high as 140 per cent. and red blood counts up to 7½ million per cmm. were found, and increased viscosity of the blood was noticeable when venepuncture was attempted. Plasma chloride was abnormally low (below 560 mgm. per cent.) in 86·1 per cent. of 43 examinations. Blood urea and blood sugar concentrations were within the normal range.

Those less severely affected were kept in bed for 12 to 36 hours, and were put on a fluid diet (milk, coffee, salt water, glucose) for 12 to 24 hours. From 4 to 5 pints of fluid were given during the first 24 hours. The moderate and severe cases were treated on the general principles for shock: warmth, fluids, stimulants, and morphia when necessary. Salt water (1 teaspoonful NaCl to 1 pint of water), milk with coffee and glucose were given orally to all conscious patients at frequent intervals—5 to 7 pints of fluid being given in the first 24 hours. When the systolic blood pressure was below 80 mm. Hg, or when vomiting occurred in hospital, oral fluids were supplemented by 2 to 4 pints of normal

saline given rectally by continuous drip. Saline was given intravenously to comatose and pulseless patients, or in moderate cases when vomiting was persistent; 20 ounces were run in rapidly, and 1 to 3 pints more were given by continuous drip. After the first 24 hours the daily fluid intake was reduced to 3 or 4 pints, and most patients took full diet 48 hours after admission.

There were no deaths in these series; the patients recovered rapidly. In cases where the pulse was imperceptible on admission, intravenous therapy evoked dramatic response; within 10 minutes the blood pressure was measurable, and in 15 minutes rose to about 90 mm. systolic and 70 mm. diastolic. Clinical signs of dehydration usually disappeared within 24 hours, and haemoconcentration, as measured by haemoglobin estimations and red blood counts, disappeared *pari passu* with the loss of signs of dehydration. In cases where the initial plasma chloride was abnormally low, 94 per cent. showed an increased concentration two to three days after collapse. Most mild cases were discharged after two days in hospital; while the moderate and severe cases were kept in bed for at least three days and discharged after four to seven days.

The relation of chloride deficiency to collapse is discussed. Plasma chloride concentrations below 560 mgm. per cent. are taken as abnormally low. [It may be noted that TALBOTT *et al.* (*Bulletin of Hygiene*, 1934, v. 9, 23) found in seven subjects an average chloride concentration of 106·4 m.-Eq. per litre of serum, which is equivalent to 622 mgm. NaCl per 100 cc. The lowest concentration recorded for any of these seven subjects was 104·8 m.-Eq. of chloride per litre, or 613 mgm. NaCl per 100 cc. of serum.] Low plasma chloride concentrations (below 560 mgm. per cent.) were found more frequently in moderate and severe cases than in mild cases. Among the mild cases low chloride concentrations appeared more frequently when there was vomiting than when there was not, and more frequently in patients with cramp than in those without cramp. It is remarked that cramp was usually associated with a plasma chloride concentration below 560 mgm. per cent. [The reviewer has examined the detailed data given by Dr. Caplan and finds that not all these conclusions have a satisfactory statistical basis. In non-collapse cases quoted in the paper the proportion of low chloride concentrations (less than 560 mgm.) is significantly smaller than in the mild cases, and the proportion of low concentrations is significantly smaller in the mild cases than in the moderate and severe group. Within the series of 170 blood examinations in mild cases, however, the proportions of high and low chloride concentrations in the two groups "cramp" and "no cramp," do not differ significantly; and, similarly, there is no significant difference between the group of cases in which vomiting occurred and that in which there was no vomiting.]

Work in the Kolar gold mines is carried on at great depths; levels 8,700 ft. below the surface are mentioned. At these depths temperatures are high. Many men work at dry bulb temperatures of 100° to about 120°F., and the wet bulb temperature is frequently between 90° and 97°F. At the deeper (and hotter) levels seasonal variations in dry bulb temperature are small, but there are substantial changes in the wet bulb temperature and in the water vapour content of the air consequent on changes of humidity at the surface. There appears to be some correlation between humidity at the surface and the incidence of cases of collapse, but it is difficult to assess the significance

of this. Cases of collapse occurred most frequently at depths of more than 5,000 ft., in dead ends supplied with upcast air of low velocity, but no information is given (and probably could not be obtained) of the "collapse rates" at different dry bulb or wet bulb temperatures.

Of the personal factors related to collapse, the more important, in order of frequency, were loss of acclimatization, disturbance of health, and lack of acclimatization. Collapse occurred in many individuals who had been absent from work for two to seven days, but whether this absence was long enough to cause loss of acclimatization is uncertain. It is noteworthy that many hundreds of thousands of man-shifts have been worked in atmospheres with wet-bulb temperatures of 90° to 97°F., without collapse occurring. Probably when a labourer finds a place too hot he refuses to work.

At the high temperatures prevailing in the Kolar gold mines the author suggests that the wet bulb temperature is a good index of comfort—high wet bulb readings are always associated with poor ventilation.

Collapse is liable to occur when the underground wet bulb temperature exceeds 90°F., and especially when it is above 93°F. Hence the engineering problem is to keep the wet bulb temperature from rising above 93°F. [The reviewer would prefer to see 90°F. as the upper limit.] Improved ventilation can do much, but at depths of 7,000 to 8,000 feet air cooling is necessary. The value of refrigeration is shown by a dramatic fall in the incidence of collapse after the installation of air-conditioning plant at the Champion Reef Mine.

[This is an important paper which deserves careful study.]

T. Bedford.

BROWN, H. R., Jr., CLARK, W. F., JONES, N., WALTHER, Johanna & WARREN, S. L. **The Relationship of Dehydration and Overhydration of the Blood Plasma to Collapse in the Management of Artificial Fever Therapy.** *J. Clin. Investigation.* 1943, July, v. 22, No. 4, 471–85, 11 figs. [37 refs.]

In 1,100 hyperpyrexial treatments between 1930 and 1937 the authors encountered many cases of collapse, with a mortality rate of 10 per cent. of their total cases. They found that these serious collapse cases were very often related to the water and salt intake and the state of hydration of the patients. The exact relationship between collapse and the water balance is not simple; serious signs are found associated usually with dehydration, but occasionally with overhydration of the blood plasma. The plasma specific gravity is used to differentiate those groups—a specific gravity over 1·0290 is taken to indicate dehydration, below 1·0255 as over-hydration.

The clinical picture of collapse is, on the whole, very similar in both groups. Accompanying the hyperpyrexia, the pulse is rapid, the systolic pressure falls, the respiration is shallow, pallor or cyanosis is present, and the extremities are cold in spite of the high temperature. Mania and later unconsciousness may supervene. Sweating and urinary excretion often cease.

The authors explain how the extreme dehydration or the waterlogging is produced, but the origin of the very similar clinical picture from those contrasted conditions is not clear. Overhydration is caused by an excessive fluid intake combined with the cessation of sweating and urinary excretion. The dehydration is produced by an inadequate

fluid intake in the presence of excessive and long-continued sweating.

By following the plasma specific gravity the authors are able to forestall the development of collapse and hence to control the water and salt intake. By this means they have greatly reduced the incidence of collapse during artificial fever therapy. *J. S. Weiner.*

BOOK REVIEWS.

ROCKEFELLER FOUNDATION. INTERNATIONAL HEALTH DIVISION. **Annual Report 1942.** pp. ix+194. With 11 figs. on 6 plates. New York: 49 West 49th Street.

This report of the activities of the International Health Division is, as usual, very readable, and serves to show the wide range of interest maintained by the Division. Many of the papers quoted have been summarized in this *Bulletin* or in the *Bulletin of Hygiene*, and the results of the work reported will be familiar to readers, but there are references to as yet unpublished work.

The subjects dealt with include yellow fever investigations in America and Africa, studies on influenza and other respiratory diseases, including atypical pneumonia, typhus, rabies, nutritional problems, malaria, tuberculosis and other diseases. There are sections on aid given by the Foundation to State and local health services, and on public health education. There is a table of expenditure.

The report is an excellent résumé of the work done, written in attractive style and with discriminating selection of essentials. It is evident that the Foundation is prepared to support research and investigation into the unexpected ramifications of any subject which engages its attention, and it is clear that such minute and assured research is usually well worth while. That the Foundation is prepared to finance large public health schemes is illustrated by its record in the elimination of *Anopheles gambiae* from Brazil; that campaign is now successfully over, but unceasing care must be taken to ensure that it does not become necessary again. In the present report work on the biology of *A. gambiae*, done during the campaign, is referred to.

The high standard of the work of the staff of the Foundation is maintained, and this report, like its predecessors, enables a reader to estimate the great scope of a great organization. *Charles Wilcocks.*

AUSTRALIA, COMMONWEALTH OF: DEPT. OF HEALTH. SERVICE PUBLICATION (SCHOOL OF PUBLIC HEALTH AND TROPICAL MEDICINE). No. 3. **Dengue. Part I. Medical** [LUMLEY, George F., M.B., Ch.M., D.T.M. (Sydney).] **Part II. Entomological** [TAYLOR, Frank H., F.R.E.S., F.Z.S.]. 171 pp. With numerous figs. & maps. 1943. Apr. 9. Glebe, New South Wales: Australasian Medical Publishing Company Ltd.

This little book may not become a best seller among the lay public of Australia for whom it was ostensibly written, but it certainly deserves a hearty welcome from the large section of the medical profession who are interested in dengue.

Part I (Medical) consists of 133 pages and has a bibliography with 140 references to publications. Each aspect of the disease is dealt with in turn; the findings and opinions of various observers are stated and then summed up by the author in an impartial and judicious manner.

Every important contribution in English has been taken into account, and as nearly all the research on the disease has been carried out by American and Australian workers the whole field is well covered. Full justice is done to the clinical and other observations by British and foreign medical men.

The striking degree of variability of the disease is clearly shown, and if the book is as widely read as it deserves to be there will be fewer reports in future years of the discovery of "new" short fevers which really are variants of dengue.

The section on the transmission of the disease to experimental animals is of special interest; the author agrees with SIMMONS that monkeys are to some degree susceptible and that many of the reported failures of attempts to reproduce the disease in these animals have been due to the use of monkeys which had lived in endemic areas where they were likely to have acquired immunity by previous attacks. In view of the possible existence of animal reservoirs of infection the term "jungle dengue" is provisionally suggested as referring to dengue in animals, but not necessarily as a parallel to the term "jungle yellow fever."

Part II (Entomological), consisting of 29 pages, contains a clear and well-illustrated description of the chief vectors, *Aëdes aegypti* and *Aëdes albopictus*.

The paper cover is quite unworthy of the contents, the title cannot be seen when the book is standing on a shelf, and there is no Index, but it is to be hoped that these drawbacks will not deprive the work of the wide publicity it deserves. *John W. D. Megaw.*

MARTINDALE. **The Extra Pharmacopoeia.** Twenty-Second Edition in Two Volumes. Vol. 2. pp. xxxiii+1217. 1943. London: The Pharmaceutical Press, 17 Bloomsbury Square, W.C.1. [27*s*. 6*d*.] [Review appears also in *Bulletin of Hygiene*.]

This second volume of the 22nd edition of "The Extra Pharmacopoeia" contains 70 more pages than the second volume of the 21st edition published in 1938. Its general scope has undergone little change, but the Editor and the Revision Committee have evidently exercised great care and judgment in the selection of new matter for notice, and in the revision of earlier matter in the light of progress of research in medicine and chemistry, to ensure that the volume contains accurate information likely to be of most value to its users.

The principal section, comprising "Analytical Addenda to Chemicals and Materia Medica in Volume I," has been brought up to date by the incorporation of alterations and amendments from the Addenda to the British Pharmacopoeia and the Supplements to the British Pharmaceutical Codex issued since 1938, as well as of information from the Pharmacopoeia of the United States, 1942, and other recently published national formularies and pharmacopoeias.

The section on "Proprietary Medicines" is prefaced by a brief historical review of efforts to secure adequate legislative control over the advertising and distribution of "patent" medicines, and gives a résumé of the essential provisions of the Pharmacy and Medicines Act, 1941, as they affect the sales of these preparations. The list of formulae which follows gives information on some 750 of them.

In revising the article on "Chemotherapy" to include the work of the last few years, the account of the development of the sulphonamide

drugs has been brought up to date by the inclusion of the main compounds of this type in use today, and by the suggestion of possible future lines of research in this series.

The application of electro-oxidation and electro-reduction to analytical problems by means of current-voltage studies has led to the inclusion of a new section on "Polarographic Analysis," a method that has been applied recently by GOODWIN and PAGE to the study of organic antimonials in relation to their leishmanicidal properties [this *Bulletin*, 1944, v. 41, 20].

The principles, apparatus and technique used in the application of spectrophotometry to analytical work are also the subject of a new section.

Some aspects of the problem of food in wartime are reviewed in the revised section on "Nutrition," to which a table giving the composition and caloric values of a large number of foods has been added. A general account of the composition and control of wartime food substitutes is also included.

The section of some 120 pages dealing with "Bacteriological and Clinical Notes with Reference to Special Diseases" has been amplified, particularly for certain bacterial and parasitic diseases likely to have an increased prevalence among men returning from service overseas. In the account of Leprosy in this section some reports claiming encouraging results from treatment with diphtheria antitoxin or toxoid are mentioned. More recent reports, however, of carefully controlled trials have led regretfully to the view that there is no pathological or clinical basis to support the diphtheria toxoid treatment for leprosy [see this *Bulletin*, 1944, v. 41, 51–2].

The short section on "Disinfectants" has been completely rewritten, and contains accounts of wartime experience in the use of antiseptics in wounds and of colloidal mists or aerosols for the sterilization of atmospheres in air-raid shelters and other crowded places.

These few notes are only an indication of the thoroughness of the revision. The whole volume provides evidence of the close and sustained labours which must have gone to its preparation under conditions prevailing during a world war. *R. L. Sheppard.*

MARTINDALE. **Supplement to the Extra Pharmacopoeia.** Twenty-Second Edition. Vol. 1. 48 pp. 1943. London: The Pharmaceutical Press, 17 Bloomsbury Square, W.C.1. [2*s*.] [Review appears also in *Bulletin of Hygiene*.]

The first volume of the 22nd edition of the Extra Pharmacopoeia was published in May 1941, since when many changes have been made in the British Pharmacopoeia, the British Pharmaceutical Codex, and the United States Pharmacopoeia and National Formulary. The principal changes, chiefly arising from war conditions and the consequent scarcity and control of ingredients, are set out in summary form in tables now issued as a Supplement to the Extra Pharmacopoeia, volume 1. The supplement also gives a résumé of recent Statutory Orders affecting supplies of drugs, etc., and lists of some new proprietary names, and of additional approved names for substances formerly known by other names. *R. L. Sheppard.*

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